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Multicenter Study of Target-Controlled Infusion of Propofol-Sufentanil or Sufentanil-Midazolam for Coronary Artery Bypass Graft Surgery

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Background: **The use of target-controlled infusions of anesthetics for coronary artery bypass graft surgery has not been studied in detail. The effects of target-controlled infusions of propofol or sufentanil, supplemented by infusions of sufentanil or midazolam, respectively, were evaluated and compared.**

Methods: **At 14 clinical sites, 329 patients were given a target-controlled infusion of propofol (n = 165) to produce effect-site concentration (C_e) of ≥3-μg/ml or a target-controlled infusion of sufentanil (n = 164). Sufentanil or midazolam, respectively, also were infused. Systolic hypertension, hypotension, tachycardia, and bradycardia were assessed by measuring heart rate and blood pressure every minute during operation. Myocardial ischemia was assessed perioperatively by monitoring ST segment deviation *via* continuous three-lead Holter electrocardiography, and it was evaluated during operation by monitoring left ventricular wall motion abnormality *via* transesophageal echocardiography.**

Results: **The measured cardiovascular parameters were satisfactory and usually similar for the patients receiving propofol-sufentanil or sufentanil-midazolam. The primary endpoint of the percentage of patients with intraoperative ST segment deviation (23 ± 6% *vs.* 24 ± 6%, $P = 0.86$) did not differ significantly between the two groups. The incidence of left ventricular wall motion abnormality shown on transesophageal echocardiography before (19 ± 4% *vs.* 26 ± 4%, $P = 0.25$) and after (23 ± 4% *vs.* 31 ± 5%, $P = 0.32$) cardiopulmonary bypass also did not differ significantly for the two groups. Changes in intraoperative target concentration were more frequent with propofol-sufentanil anesthetic than with sufentanil-midazolam (11.7 ± 7.1 *vs.* 7.3 ± 3.6, $P < 0.001$). The incidence of intraoperative hypotension (77% *vs.* 55%, $P < 0.001$), the use of inotropic/vasopressor medications (93% *vs.* 84%, $P = 0.01$), and the administration of crystalloids (2.8 ± 1.4 L *vs.* 2.4 ± 1.2 L, $P < 0.001$) were significantly greater in the propofol-sufentanil group. Conversely, the incidence of intraoperative hypertension (43% *vs.* 54%, $P = 0.05$) and the use of antihypertensive/vasodilator medications (70% *vs.* 90%, $P < 0.001$) were significantly less in the propofol-sufentanil group.**

Conclusions: **Target-controlled infusions of propofol or sufentanil, supplemented by infusions of sufentanil or midazolam, respectively, were suitable to provide anesthesia for coronary artery bypass graft surgery. Continuous monitoring revealed a high prevalence of hemodynamic abnormalities. Despite greater hypotension in the propofol-sufentanil group and greater hypertension in the sufentanil-midazolam group, episodes of myocardial ischemia were similar for both groups and were not temporally related to episodes of hemodynamic abnormalities. (Key words: Anesthesia: cardiac. Anesthetics, intravenous: midazolam; propofol; sufentanil. Anesthetic techniques: computer-assisted continuous infusion. Heart: hemodynamics; infarction; ischemia. Monitoring: electrocardi-**

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ography; Holter electrocardiography; transesophageal echocardiography. Surgery: cardiac; coronary artery bypass graft.)

TO provide anesthesia for coronary artery bypass graft (CABG) surgery, an opioid is usually delivered in combination with a hypnotic drug or a potent inhalational anesthetic.[1,2] A target-controlled infusion is desirable for administering an intravenous anesthetic.[3] Rapid emergence from sufentanil anesthesia, combined with its potency, make it an opioid of choice for CABG surgery. For infusion, propofol and midazolam are two of the most commonly used hypnotic drugs. Target-controlled infusions of propofol and sufentanil may be useful for CABG surgery. However, the effects on cardiovascular parameters of anesthetics administered by target-controlled infusion during all stages of CABG surgery are unknown.

Target-controlled infusion of propofol when combined with an opioid[4] or nitrous oxide[5] may cause hypotension[4,5] and bradycardia.[4] Patients with coronary artery disease may be especially susceptible to myocardial ischemia and other adverse effects of hypotension.[6] Although the use of propofol and opioids during CABG surgery is reported to be associated with acceptable hemodynamics at certain stages of CABG surgery,[1,2] hemodynamic abnormalities detected by continuous observation throughout surgery have not been described.

This study evaluated and compared the cardiovascular responses to two anesthetic regimens using target-controlled infusion of propofol or sufentanil. As clinically indicated, supplementation was provided with sufentanil or midazolam infusion, respectively. The primary endpoint for comparing the two groups was the percentage of patients with intraoperative ST segment deviation. We also determined the occurrence of tachycardia, bradycardia, systolic hypertension, and hypotension from heart rate and blood pressure recorded every minute during operation. For the two anesthetic regimens, we determined the number of intraoperative target concentration changes; the use of cardiovascular medications; the occurrence of ischemic changes detected by continuous perioperative electrocardiography (ECG) and continuous intraoperative transesophageal echocardiography (TEE); myocardial infarction (MI); and major adverse clinical events.

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Materials and Methods

Study Participants

After obtaining institutional approval and written informed consent from participants, we enrolled 329 patients undergoing CABG surgery at 14 academic medical centers in the United States (appendix I) during the period from June 1992 through December 1993. To be included in the study, patients had to be at least 35 yr old, be scheduled for nonemergent CABG surgery with no other planned surgical procedure, and have a left ventricular ejection fraction greater than 25%, at least 50% stenosis of the left main coronary artery, or at least 70% stenosis of two or more major coronary arteries. We excluded patients with preoperative evolving MI, increased serum concentrations of creatine kinase myocardial band (CK-MB), hemodynamic instability with systolic blood pressure (SBP) less than 90 mmHg, cardiogenic shock, unsuccessful coronary angioplasty within 24 h before surgery, ECG uninterpretable for S-T segment deviation due to cardiac conduction changes or use of a ventricular pacemaker, or esophageal disease that precluded placement of a TEE probe.

Patients meeting these criteria were randomly assigned to receive either a target-controlled infusion of open-label propofol (n = 165) and an infusion of sufentanil, or target-controlled infusion of open-label higher-dose (*vide infra*) sufentanil (n = 164) and an infusion of midazolam.

Anesthetic Management

Lorazepam (1 to 4 mg) was administered orally the evening before surgery. Morphine sulfate (0 to 0.2 mg/kg given intramuscularly or intravenously) and midazolam (0 to 0.1 mg/kg given intramuscularly or intravenously) were administered 60 to 90 min before surgery. Usual cardiac medications were continued until surgery.

For sedation during catheter placement before induction of anesthesia, patients in the propofol-sufentanil group were eligible to receive an infusion of propofol to a target plasma concentration of 0.25 to 0.75 μg/ml. Patients in the sufentanil-midazolam group were eligible to receive 0 to 0.05 mg/kg midazolam intravenously for sedation.

A Harvard 22 computer-controlled pump (Harvard Apparatus, South Natick, MA) was used to produce the desired target plasma concentration (C_p) or effect-site concentration (C_e) of propofol or sufentanil. At 13 of the 14 clinical sites, STANPUMP software|||| was used

to apply pharmacokinetic models of propofol## or sufentanil.[7] One site, Duke University, used Computer Assisted Continuous Infusion (CACI) II software.*** The pharmacokinetic parameters employed by CACI II for sufentanil[7] were identical to those used by the other sites, but the pharmacokinetic parameters used by CACI II for propofol[8] were slightly different. The infusion software recorded the times, rates of drug infusion, and the predicted C_p and C_e. The other anesthetic (sufentanil or midazolam, respectively) was infused through a constant-rate pump that did not keep an automated record. The total doses of the anesthetics administered were recorded.

For the propofol-sufentanil group, C_p was at least 3 μg/ml during induction of anesthesia, and C_e was at least 3 μg/ml during maintenance of anesthesia. If the depth of anesthesia required adjustment, C_e was changed in 0.5- to 1-μg/ml increments in the range of 3 to 10 μg/ml. During induction, as clinically indicated, a 0- to 0.5-μg/kg bolus of sufentanil was administered. During maintenance, as clinically indicated, sufentanil was infused at a rate of 0 to 0.6 $\mu g \cdot kg^{-1} \cdot h^{-1}$ for the first 2 h, decreased by 0.1 $\mu g \cdot kg^{-1} \cdot h^{-1}$ for the next 3 h, and decreased again by 0.1 $\mu g \cdot kg^{-1} \cdot h^{-1}$ thereafter. When a change in anesthetic administration was required due to hemodynamic changes, the administration of propofol was varied within the protocol limits before sufentanil administration was altered.

For the sufentanil-midazolam group, the baseline sufentanil C_e was 3 ng/ml from induction of anesthesia until cardiopulmonary bypass (CPB), 1 ng/ml during CPB, and 0.6 ng/ml after CPB. If adjustment in the depth of anesthesia was required, C_e was changed in 0.5- to 1-ng/ml increments in the range of 0.6 to 6 ng/ml. The baseline rate for infusion of midazolam was 30 $\mu g \cdot kg^{-1} \cdot h^{-1}$ from induction of anesthesia to skin closure. If an increase in the depth of anesthesia was required, a 0- to 20-μg/kg bolus of midazolam was administered, followed by an increase in the infusion of 0 to 6 $\mu g \cdot kg^{-1} \cdot h^{-1}$. If clinically indicated, infusion of midazolam could be decreased or discontinued. When a change in anesthetic administration was required because of hemodynamic changes, the administration of sufentanil was varied within the protocol limits before the administration of midazolam was altered.

Both groups were given vecuronium for neuromuscular blockade. Antiischemic medications such as nitrates and calcium-channel blockers were given only if the following indicators of ischemia occurred: new ST segment deviation, new left ventricular wall motion abnormality, or increased pulmonary artery pressure. After operation, both groups were given morphine and midazolam for analgesia and sedation.

Cardiovascular Medications

The cardiovascular medications administered before, during, and up to the first day after operation were recorded. Because of the many medications used, the data were tabulated as the percentage of patients receiving each class of medications during each period.

Hemodynamic Monitoring

We determined baseline values for noninvasive SBP and heart rate (HR) by averaging three values obtained at rest before operation. During operation, SBP obtained *via* arterial cannula and HR were recorded every minute using ARKIVE (Diatek, San Diego, CA) and the monitoring equipment at the clinical site. A pulmonary artery catheter was used to determine cardiac output and pulmonary artery pressures.

For the prebypass period, hypertension was defined as SBP greater than 120% of the preoperative baseline value. According to the protocol, hypertension was treated by increasing the dose of anesthetic and, if necessary, by infusing sodium nitroprusside. Hypotension, defined as SBP less than 80% of the baseline, was treated by reducing the dose of anesthetic and administering fluids, phenylephrine, ephedrine, epinephrine, dopamine, or calcium chloride. Tachycardia, defined as HR greater than 120% of baseline, was treated by increasing the dose of anesthetic or infusing esmolol. Bradycardia, defined as HR less than 80% of the baseline, was treated if clinically indicated.

During CPB, mean arterial pressure was maintained between 40 and 80 mmHg by changing the depth of anesthesia or administering phenylephrine or sodium nitroprusside. After CPB, the limits for hypertension, hypotension, tachycardia, and bradycardia were defined as 140 mmHg, 90 mmHg, 100 beats/min, and 60 beats/min, respectively. The ventricular rate, whether paced or intrinsic, was used to detect episodes of tachycardia and bradycardia. Treatment of hemodynamic abnormalities was similar to that in the pre-CPB period.

An episode of HR or SBP abnormality was diagnosed if at least four of five consecutive per-minute HR or

Dyck JB, Varvel J, Hung O, Shafer SL: The pharmacokinetics of propofol vs. age (abstract). ANESTHESIOLOGY 1991; 75:A315.

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SBP samples exceeded the threshold. If a sample less than 5 min after an episode also exceeded the threshold, the episode was extended to that sample. Two investigators (appendix II) independently evaluated the SBP and HR data to identify episodes of abnormality. Any differences between them were resolved in consultation with a third investigator. We determined the percentage of patients having episodes of HR or SBP abnormality and the duration of such episodes per hour of monitoring for the pre-CPB, CPB, and post-CPB periods and for the entire intraoperative period.

Holter Electrocardiography

To compare the two groups, we specified the primary endpoint as the percentage of patients who had intraoperative episodes of ST segment depression or elevation. We used a three-channel amplitude modulated Holter monitor (series 8500; Marquette Electronics, Milwaukee, WI) to continuously record modified bipolar leads CM_5, CC_5, and ML.[9] Recording usually started the evening before surgery and continued for 48 h afterward. The total duration of monitoring was divided into preoperative, pre-CPB, CPB, post-CPB, and postoperative periods.

Holter ECG recordings were screened using a Marquette SXP Laser Holter scanner. The ECG data obtained by one investigator (level I) were verified by two additional investigators (levels II and III). A duration of Holter monitoring was said to be uninterpretable if identification of ischemic ST segment deviation was not done because of noise; ventricular pacing; or change in cardiac conduction, that is, left bundle branch block, intraventricular conduction defect, or superior QRS axis (rS complexes in all the monitored leads). Because only lateral and inferior leads were used during monitoring, the occurrence of ST segment deviation was determined during right bundle branch block. The durations of right bundle branch block and uninterpretable ECG due to ventricular pacing and cardiac conduction change were determined.

An episode of ST segment deviation was defined as a new ischemic ST segment deviation of at least 1 mm from local baseline, which lasted at least 1 min and was separated from other episodes by at least 1 min.[10-13] We recorded the HR at the local baseline and at onset of the episode, duration of the episode, and the new ST segment deviation-duration integral (*i.e.*, area under the curve).

For each perioperative period and for each of the two groups, we determined the percentage of patients in whom an episode of ST segment depression or elevation began during that period.[14] To determine the severity of ischemia, during each period and for each patient, we divided the number of episodes of ST segment deviation that had onset, the total minutes of ST segment deviation, and the area under the curve by hours of data interpretable for ST segment deviation. If an episode continued from one period to another, the portion of the episode occurring in each period was assigned to that period when determining duration and area under the curve of ST segment deviation. During CPB, ST segment deviation was determined when the QRS complex was present before and after cardioplegic arrest.

Transesophageal Echocardiography

From induction of anesthesia to chest closure, a TEE probe recorded the midpapillary short-axis view of the left ventricle during cardiac contractions. For the pre-CPB period, we analyzed 60-sec samples of TEE recordings obtained every 15 min and at other times of clinical interest listed elsewhere.[9] For the post-CBP period, we analyzed samples obtained every 5 min.[9] Using papillary muscles as the landmarks, we divided the images into four segments: posterior, septal, anterior, and lateral. The wall motion in each segment was graded as follows: 0 = normal wall motion, 1 = mild hypokinesia, 2 = severe hypokinesia, 3 = akinesia, and 4 = dyskinesia. For each patient, the lowest score for each segment before CPB was used as baseline. An episode of wall motion abnormality was defined as worsening of the wall motion of any segment by two or more grades for at least 1 min.[9] The analysis performed by one investigator was verified by another investigator. Any differences between them were resolved in consultation with a third investigator, if necessary. The interexamination variability in our laboratory is within acceptable limits.[9]

Myocardial Infarction

Q wave MI was defined as the occurrence of a significant new perioperative Q wave on 12-lead ECG. Electrocardiograms were recorded before operation, when patients arrived in the intensive care unit after surgery, in the morning on postoperative days 1 and 2, and when clinically indicated. Each ECG was analyzed by two physician-electrocardiographers (appendix II) using the Minnesota Code.[15] The ECGs of patients who were judged by either electrocardiographer as having definite, probable, or possible MI were re-

viewed by three additional electrocardiographers, whose majority vote determined the presence or absence of "Q wave MI."

We measured CK and its myocardial fraction (CK-MB) before operation, when patients arrived in the intensive care unit after surgery, and every 8 h for 48 h thereafter. Creatine kinase myocardial band values were determined at the clinical sites; 13 sites used electrophoresis to detect CK-MB activity (U/l), and three sites used immunoassay to measure CK-MB mass (μg/l). Concentrations of CK-MB exceeding 100 U/l or μg/l were considered indicative of "CK-MB MI." These two thresholds, although different, were used in the absence of other widely applied thresholds.

Other Adverse Cardiovascular Outcomes

We also recorded the occurrence of other adverse postoperative cardiovascular outcomes[14]: death caused by cardiac arrest or any other cause, unstable angina, congestive heart failure, use of intraaortic balloon counterpulsation, stroke, and intraoperative recall. Unstable angina was defined as precordial pain that lasted 30 min or more and that was unresponsive to rest and nitroglycerin and associated with transient ST-T segment changes on ECG without the occurrence of MI. The occurrence of congestive heart failure was determined by signs, symptoms, and radiographic evidence of pulmonary congestion requiring administration of diuretics, or by evidence of new or worsening ventricular failure (cardiac index $\leq 2\ l \cdot min^{-1} \cdot m^{-2}$) requiring intraaortic balloon counterpulsation. Stroke was defined by the presence of a persistent focal central nervous system defect that was confirmed by computed tomography or magnetic resonance imaging.

Statistical Analysis

We used the statistical software program SAS (version 6.09; SAS Institute, Cary, NC) on the UNIX platform. For two-group comparison of demographic and clinical data that were discrete variables, we applied the Cochran-Mantel-Haenszel test adjusted for center. For continuous variables, we used the general linear model. When statistically significant, center and center-by-group interactions were retained in the model equation. Probability values were provided by *F* test on the sums of squares that were adjusted for center effect when the adjustment was statistically significant. A *P* value ≤ 0.05 on a two-tailed test was considered significant. When appropriate, a natural logarithmic transformation of the data was performed before calculating the *F* test. The *Z* approximation was used to test the difference between two proportions. The incidence of intraoperative ischemic ST segment deviation was the primary outcome of this study. We did not correct for multiple comparisons between the two groups.

Results

Demographic and clinical characteristics were similar for the two groups (table 1). The propofol-sufentanil group required more intraoperative administration of crystalloids.

Infusion of Anesthetics

To induce anesthesia, the propofol-sufentanil group received 1.5 ± 1 mg/kg propofol and 0.4 ± 0.2 μg/kg sufentanil, and the sufentanil-midazolam group received 4.3 ± 2 μg/kg sufentanil and 12.9 ± 15.1 μg/kg midazolam. The total intraoperative doses were 32.6 ± 11.9 mg/kg propofol and 2.4 ± 0.8 μg/kg sufentanil in the propofol-sufentanil group, and 19 ± 7.8 μg/kg sufentanil and 160 ± 60 μg/kg midazolam in the sufentanil-midazolam group.

STANPUMP anesthetic infusion records were available for 131 patients in the propofol-sufentanil group and for 126 patients in the sufentanil-midazolam group. Computer Assisted Continuous Infusion records were available for ten patients in the propofol-sufentanil group and for nine patients in the sufentanil-midazolam group. These records were used to derive the predicted C_e and mean infusion rates for the target-controlled infusions (fig. 1). The mean C_e for propofol was nearly 3 μg/ml, the minimum required by the protocol. In the sufentanil-midazolam group, the C_e for sufentanil during and after CPB was less than the C_e before CPB but greater than the minimum required by the protocol.

The C_e was changed more often for propofol than for sufentanil, during induction of anesthesia (1.4 ± 0.7 *vs.* 1.0 ± 0.1, $P \leq 0.01$), tracheal intubation (1.2 ± 1.6 *vs.* 0.5 ± 0.8, $P \leq 0.01$), and the entire intraoperative period (11.7 ± 7.1 *vs.* 7.3 ± 3.6, $P \leq 0.001$).

Cardiovascular Medications

During operation, a greater percentage of patients in the propofol-sufentanil group was given inotropic/vasopressor medications, whereas a greater percentage of patients in the sufentanil-midazolam group was given antihypertensive/vasodilator medications, in-

Table 1. Demographic and Clinical Characteristics of Patients in the Propofol–Sufentanil and Sufentanil–Midazolam Groups

Characteristic	Propofol–Sufentanil Group (n = 165)	Sufentanil–Midazolam Group (n = 164)
History		
Age (yr)	63.5 ± 9.8	64.4 ± 9.5
Body surface area (m^2)	1.96 ± 0.21	1.95 ± 0.18
Female gender	18%	18%
Unstable angina	47%	53%
Prior MI	39%	39%
Prior MI within 3 months	15%	16%
Hypertension	61%	60%
Congestive heart failure	12%	5%
Diabetes mellitus type I	7%	10%
Diabetes mellitus type II	10%	10%
Previous CABG Surgery	12%	9%
Previous PTCA	16%	19%
Angiographic Results		
Stenosed coronary arteries:		
Left main artery ≥ 50%	21%	18%
Two major arteries ≥ 70%	39%	38%
All three major arteries ≥ 70%	45%	41%
Ejection fraction (%)	56 ± 14	54 ± 14
Left ventricular end-diastolic pressure (mmHg)	15 ± 6	17 ± 7
Medications		
Preoperative morphine (mg/kg)	0.10 ± 0.03	0.11 ± 0.03
Preoperative midazolam (mg/kg)	0.05 ± 0.02	0.05 ± 0.02
Preinduction propofol ($mg \cdot kg^{-1} \cdot h^{-1}$) (duration 31 ± 19 min for 68 patients)	2.3 ± 2.4	—
Preinduction midazolam (mg/kg) (75 patients)	—	0.03 ± 0.02
Clinical course		
Number of grafts	3.4 ± 1.0*	3.1 ± 1.1
Duration of CPB (min)	104 ± 34	100 ± 38
Duration of aortic occlusion (min)	59 ± 24	56 ± 24
Duration of postoperative intubation (h)	14.3 ± 4.9	16.4 ± 4.7
Surgeon's assessment: poor revascularization	0%	1%
Blood cardioplegia	76%	82%
Intraoperative fluids		
Crystalloids (ml)	2,812 ± 1,433*	2,422 ± 1,248
Colloids (ml)	395 ± 495	412 ± 491
Packed red blood cells (ml)	301 ± 493	266 ± 528

Values are mean ± SD or percentage of patients having the characteristic. CABG = coronary artery bypass graft; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; CPB = cardiopulmonary bypass.

* Significant ($P \leq 0.05$) difference between the two groups.

cluding diuretics, β-blockers, and calcium-channel blockers (table 2). After operation, antihypertensive/vasodilator medications were used more commonly for the propofol-sufentanil group (99% *vs.* 95%, $P < 0.05$). In both groups, the percentage of patients given β-blockers, calcium-channel blockers, or nitrates tended to be greater before surgery than after surgery. In both groups, the postoperative use of diuretics tended to be greater than the intraoperative use, which tended to be greater than the preoperative use.

Hemodynamic Changes

Intraoperative hemodynamic data recorded every minute were available for 155 and 152 patients, respectively, in the propofol-sufentanil and sufentanil-midazolam groups. There were no significant differences in HR between the two groups during induction, intubation, incision, or sternotomy. The propofol-sufentanil group had lesser SBP during intubation (117 ± 24 *vs.* 124 ± 23 mmHg, $P = 0.02$) and incision (113 ± 19 *vs.* 118 ± 18 mmHg, $P = 0.05$). Before and after CPB, 73%

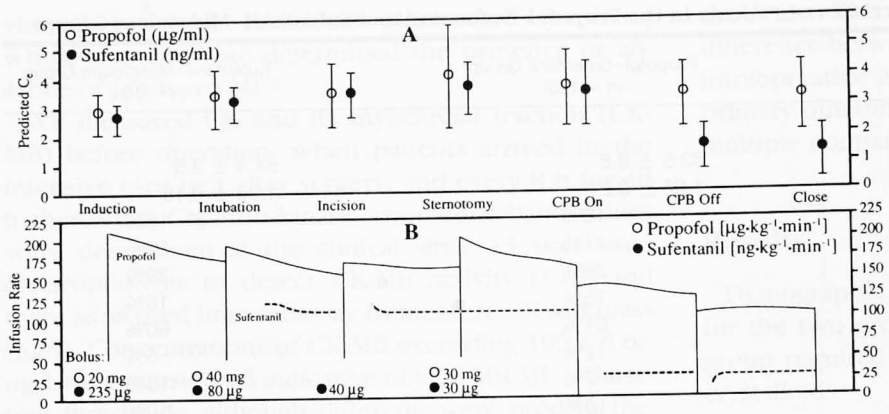

Fig. 1. Data are presented for the target-controlled infusions; that is, propofol and sufentanil, respectively, in the two groups, at various stages during coronary artery bypass graft surgery. (*A*) The predicted (mean ± SD) target effect-site concentration (C_e). (*B*) Mean rates of drug infusion. A rapid infusion was listed as a bolus. In the sufentanil-midazolam group, at the onset of cardiopulmonary bypass, no sufentanil administration was required for an average of 35 min, whereas after cardiopulmonary bypass, no sufentanil administration was required for an average of 6 min.

and 89% of the propofol-sufentanil group had SBP less than 90 mmHg for at least 1 min; 5.7% ± 8.9% and 17.8% ± 17.2% of the observations for these patients were less than 90 mmHg. In the sufentanil-midazolam group, before and after CPB, 65% and 79% of the patients had SBP less than 90 mmHg for at least 1 min; 4.4% ± 8.4% and 10.8% ± 14% of the observations for these patients were less than 90 mmHg.

The percentage of patients with protocol-defined episodes of hypotension was greater in the propofol-sufentanil group in all periods (fig. 2A). The percentage of patients with episodes of hypertension was greater in the sufentanil-midazolam group in the post-CPB and total intraoperative periods (fig. 2A). The total intraoperative duration of episodes of hypotension was greater for the propofol-sufentanil group and duration of episodes of hypertension was greater for the sufentanil-midazolam group (fig. 2B). The occurrence of tachycardia or bradycardia did not differ significantly between the two groups (fig. 2). There were no clinically important differences in cardiac output or pulmonary artery pressures between the two groups.

Ischemic Changes on Holter ECG

Continuous (Holter) ECG data were obtained for 142 patients in the propofol-sufentanil group and for 152 patients in the sufentanil-midazolam group. The primary endpoint, the percentage of patients having intraoperative ST segment deviation (23% ± 6% *vs.* 24% ± 6%, $P = 0.86$), did not differ significantly for the two groups. In addition, the percentage of patients having S-T segment deviation during or after surgery (29% ± 6% *vs.* 36% ± 6%, $P = 0.20$) did not differ significantly for the two groups.

The durations of interpretable and uninterpretable periods on ECG (fig. 3A), the percentage of patients who

Table 2. Percentage of Patients Given Cardiovascular Medications during Various Periods

	Preoperative		Intraoperative		Postoperative Day #0,1	
Medications	Propofol–Sufentanil Group	Sufentanil–Midazolam Group	Propofol–Sufentanil Group	Sufentanil–Midazolam Group	Propofol–Sufentanil Group	Sufentanil–Midazolam Group
β-blockers	53	55	14	18	42	37
Calcium-channel blockers	56	50	7	4	38*	28
Nitroprusside	0	1	42*	67	77	73
Nitrates	64	60	28	23	44	38
Diuretics	18*	10	37	39	67	73
Other antihypertensives/vasodilators	24	23	1	3	28	20
Any of the above	94	92	70*	90	99*	95
Antiarrhythmics	13*	7	47	44	21	15
Inotropes/vasopressors	0	1	93*	84	58	52

* Significant ($P \leq 0.05$) difference between the two groups.

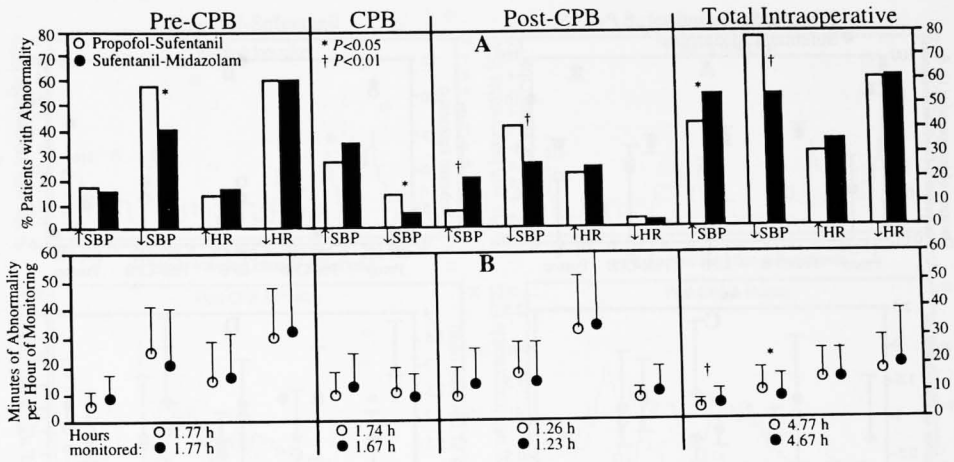

Fig. 2. (*A*) The percentage of patients who had episodes of hemodynamic abnormality: hypertension (↑SBP), hypotension (↓SBP), tachycardia (↑HR), and bradycardia (↓HR). (*B*) The minutes of hemodynamic abnormality per hour of monitoring; before, during, and after cardiopulmonary bypass, and during the entire intraoperative period. The mean hours of monitoring for each period are also listed. Values in *B* are presented as means and standard deviations for all patients in each group. Differences between the propofol-sufentanil and sufentanil-midazolam groups are significant at *$P \leq 0.05$ and †$P \leq 0.01$.

had ST segment deviation starting in each period (fig. 3B), and the number of episodes of ST segment deviation starting per hour in each period (fig. 3C) were similar for the two groups. For both groups, ST segment elevation tended to have greater absolute value than ST segment depression (fig. 3D). For both groups, the duration (fig. 3E) and area under the curve (fig. 3F) per hour of ST segment deviation tended to be greater during operation, especially in the post-CPB period. For both groups, mean HR at the onset of ST segment deviation tended to increase progressively during operation and to be highest after operation (fig. 3G). For both groups, HR at the onset of ST segment deviation generally was 5 to 10 beats/min greater than the HR at the local baseline (fig. 3H). However, for both groups, a substantial number of episodes, especially during CPB, occurred with a reduction in HR (fig. 3H).

Because ST segment deviation was most prevalent in the CPB and post-CPB periods (fig. 3), the percentage of patients who had ST segment depression or elevation at any time during Holter ECG monitoring after release of aortic occlusion was determined (fig. 4). The pattern was similar for both groups, with ST segment deviation primarily occurring in the first 8 h after release of aortic occlusion.

Multiplying the number of episodes of ST segment deviation for each patient by the number of episodes of hemodynamic abnormality and adding this for all 307 patients who had the required hemodynamic and Holter ECG data yielded a possible maximum of 2,052 overlaps. No trend was identified in the 69 overlaps observed.

Left Ventricular Wall Motion Abnormalities

Intraoperative left ventricular wall motion abnormalities detected *via* TEE were similar for the two groups (table 3). For both groups, unlike left ventricular wall motion abnormality (table 3), ST segment deviation was more common after CPB than before CPB (fig. 3).

Other Adverse Outcomes

One patient in the propofol-sufentanil group died perioperatively of cardiac causes. The incidence of Q wave MI was 7% in the propofol-sufentanil group and 4% in the sufentanil-midazolam group. The incidence of CK-MB $\geq$ 100 U/l or μg/l was 7% in the propofol-sufentanil group and 6% in the sufentanil-midazolam group. New postoperative unstable angina or congestive heart failure was not diagnosed in any patient. Intraaortic balloon counterpulsation was used for two patients in the propofol-sufentanil group and four patients in the sufentanil-midazolam group. Stroke was diagnosed in one patient in each group. None of the patients reported intraoperative awareness.

Discussion

Our randomized trial demonstrates that anesthetic regimens based on target-controlled infusions of propofol or sufentanil, supplemented by sufentanil or midazolam, respectively, are suitable for CABG surgery. Because a single anesthetic agent is not suitable in clinical practice,[3] combinations of anesthetic agents were administered.

The primary endpoint, the percentage of patients having intraoperative ST segment depression or elevation (23% ± 6% vs. 24% ± 6%, $P = 0.86$), was not significantly different for the propofol-sufentanil and sufentanil-midazolam groups. Systolic blood pressure and HR observed every minute during operation revealed that abnormalities were more common than

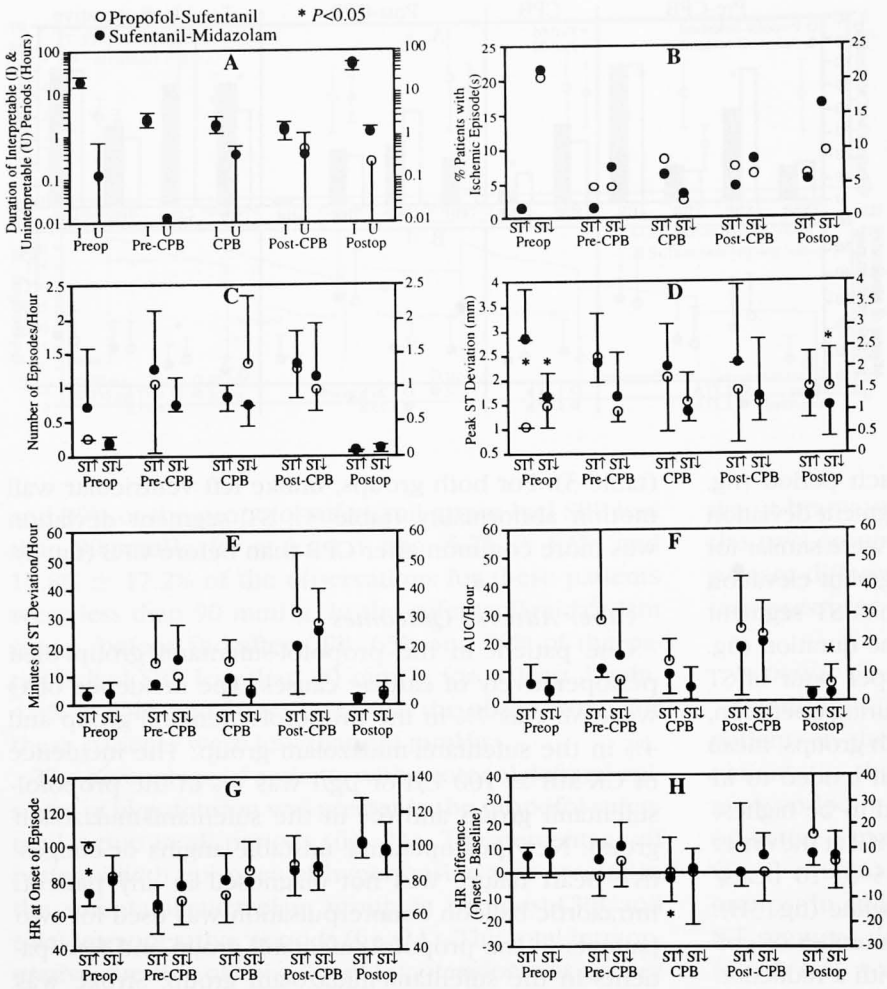

Fig. 3. The parameters of ST segment depression (↓ST) and ST segment elevation (↑ST) during preoperative (Preop), pre-cardiopulmonary bypass (Pre-CPB), CPB, post-CPB, and postoperative (Postop) periods, for patients in the propofol-sufentanil and sufentanil-midazolam groups. Panels *C, E,* and *F* show means and standard deviations only for patients who had ST segment deviation in a given period, whereas *A* presents data for all patients. Sometimes mean values for the two groups are so close that their graphic displays overlap. I = Period when Holter electrocardiogram is interpretable for ST segment deviation. U = Period when Holter ECG is uninterpretable for ST segment deviation. AUC = Area under the curve; that is, ST segment deviation-duration integral. HR = Heart rate. Differences between the two groups are significant at $P \leq 0.05$.

those reported previously during cardiac surgery,[1,2] although hypotension and bradycardia were less common than those expected on the basis of studies of target-controlled propofol infusion.[4,5] The propofol-sufentanil group had greater incidence of hypotensive episodes and use of inotropic/vasopressor medications and crystalloids, and more changes in target propofol concentration. The sufentanil-midazolam group had greater incidence of hypertensive episodes and use of antihypertensive/vasodilator medications. The episodes of ST segment deviation were not temporally associated with protocol-defined episodes of abnormal SBP or HR. Because the data were collected from 14 clinical sites throughout the nation, the results should have wide applicability.

Anesthetic Administration

For lower abdominal surgery in women younger than our population, who were given benzodiazepine premedication, a plasma concentration of propofol of 3.5 μg/ml was reported to lead to fastest recovery when alfentanil was also given.[16] For major surgery in patients who were not given premedication, a plasma concentration of propofol of 4 ± 1 μg/ml was reported to be required when propofol was given with an opioid.[17] The plasma concentration of propofol was measured at several intraoperative stages for 11 of our patients at Emory University.[18] The measured concentration was greater than the intended concentration, especially in the pre-CPB period, when it was approximately double the intended concentration.[18] This occurred in part because the pharmacokinetic parameters for CABG surgery are different from those for noncardiac surgery.[18] Greater-than-intended concentration of propofol may in part explain the high incidence of hypotension observed in the propofol-sufentanil

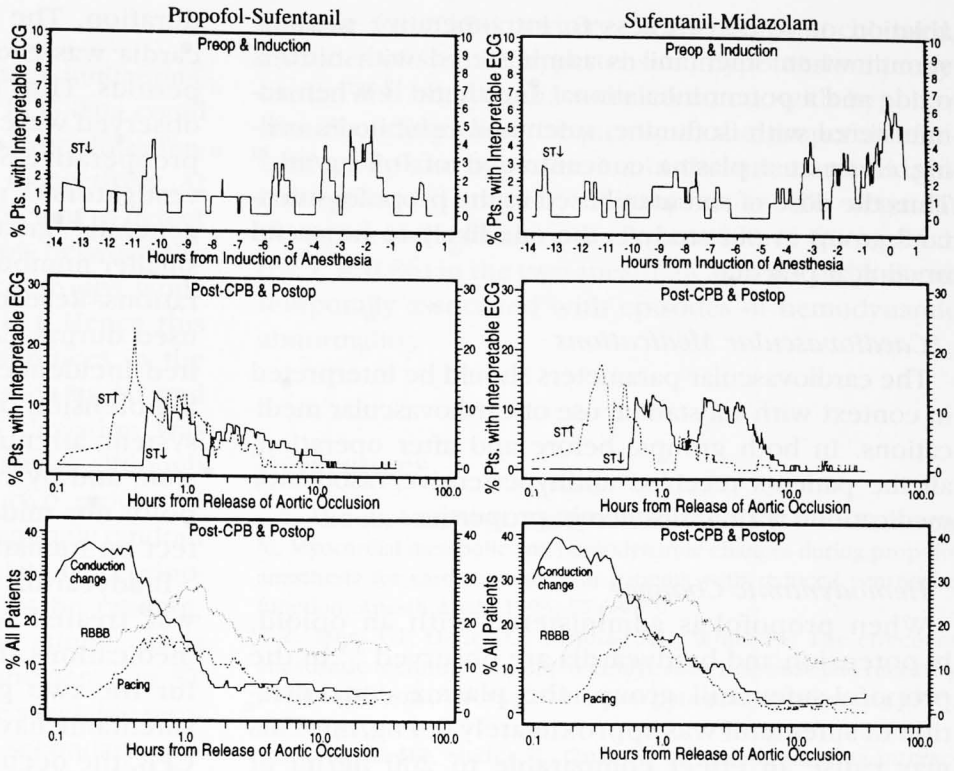

Fig. 4. For the propofol-sufentanil or sufentanil-midazolam groups, the temporal distribution of percentage of patients with Holter electrocardiograms interpretable for ST segment deviation who had ST segment depression (↓ST) or ST segment elevation (↑ST). Also presented is the temporal distribution after release of aortic occlusion of the percentage of all patients with right bundle branch block, ventricular pacing, or cardiac conduction changes making the Holter electrocardiogram uninterpretable for ST segment deviation. Before cardiopulmonary bypass, only ST segment depression was common and is presented.

group. The target concentration of propofol was chosen based on data derived during noncardiac surgery and may not be optimal for CABG surgery. Patients in the propofol-sufentanil group were given 0.05 ± 0.02 mg/kg (3.9 ± 1.8 mg) midazolam 60 to 90 min before surgery. The presence of midazolam could have contributed to the hypotension observed in the propofol-sufentanil group. The amnesic properties of midazolam that would allow infusion of propofol to be decreased during hypotension without risking recall were not used in this study.

The estimated plasma concentration of sufentanil in the propofol-sufentanil group was 0.38 to 0.45 ng/ml. This is the concentration reported to be required for

Table 3. Left Ventricular Wall Motion Abnormalities Detected by Transesophageal Echocardiography

Characteristic	Before Cardiopulmonary Bypass		After Cardiopulmonary Bypass	
	Propofol–Sufentanil Group	Sufentanil–Midazolam Group	Propofol–Sufentanil Group	Sufentanil–Midazolam Group
No. of evaluated patients	104	96	100	97
Hours monitored	1.4 ± 0.6	1.3 ± 0.5	0.9 ± 0.3	0.9 ± 0.3
No. of patients with abnormality	20	25	23	30
Minutes of abnormality per hour of monitoring†	10.2 ± 8.9	14 ± 10.6	14.7 ± 8.3	19.4 ± 10.7
Average duration of episode (min)	11.9 ± 10.8	12.9 ± 8.4	11.9 ± 8.2	16.6 ± 13.8
Number of patients with abnormality in:				
Posterior wall	9	17	7*	20
Septum	7	11	7	8
Anterior wall	4	3	10	12
Lateral wall	2	1	5	5

Values are mean ± SD.

* Significant ($P \leq 0.05$) difference between the two groups.

† Only for patients with abnormality.

ablation of responsiveness to intraoperative noxious stimuli when sufentanil is administered with nitrous oxide and a potent inhalational anesthetic.[19] When administered with isoflurane, sufentanil exhibited a ceiling effect at a plasma concentration of 0.5 ng/ml.[20] Thus the dose of sufentanil used in the propofol-sufentanil group in our study is the one likely to be useful in clinical practice.

Cardiovascular Medications

The cardiovascular parameters should be interpreted in context with substantial use of cardiovascular medications. In both groups, before and after operation, all the patients received antihypertensive/vasodilator medications with antiischemic properties.

Hemodynamic Changes

When propofol is administered with an opioid, hypotension and bradycardia are observed.[4,5] In the propofol-sufentanil group, the plasma concentration of sufentanil was approximately 0.4 ng/ml. This may cause an effect comparable to 200 ng/ml of alfentanil.[19] Combined with 3.6 μg/ml of propofol, this may cause a reduction in SBP and HR exceeding 20% compared with preinduction values in unpremedicated patients.[4] Our patients may have even lower SBP and HR because of advanced age, premedication, and preoperative and intraoperative cardiovascular medications, including β-adrenergic and calcium-channel blockers.

In healthy young volunteers given propofol with nitrous oxide, to prevent movement in response to noxious stimuli on 95% of the occasions, an effect-site concentration of 9.7 μg/ml was required, which reduced the SBP by about 50% from the preinduction value.[5]

In our study, the threshold for hypotension and bradycardia was a 20% reduction in SBP and HR compared with the preoperative values. Systolic blood pressure was used instead of diastolic or mean blood pressure because in clinical practice it is common to follow SBP. Because the baseline SBP value was obtained noninvasively and the intraoperative SBP values were obtained *via* an arterial catheter, a small difference in the value of SBP occurred. This is unlikely to have altered our conclusions regarding hemodynamic changes. In the propofol-sufentanil group, SBP was less than the threshold for less than 50% of pre-CBP duration, and HR was less than the threshold for slightly more than 50% of the pre-CBP duration. The duration of hypotension and bradycardia was even less during the CPB and post-CPB periods. Thus the hypotension and bradycardia we observed were less than those predicted.[4,5] We used preoperative SBP and HR as the baseline; other investigators[4,5] used preinduction values that were generally greater. Their results are based on a smaller number of patients observed for smaller durations. Researchers doing other studies of propofol used during CABG surgery have reported only limited incidences of hypotension.[1,2] Propofol causes hypotension by inhibiting the sympathetic nervous system, attenuating the reflex response to hypotension, and by causing vasodilation.[21-23] Neither propofol nor midazolam have a negative inotropic effect on human atrial muscle.[24]

Bradycardia was rare after CPB, in part because it was treated with cardiac pacing or chronotropic medications. Heart rate did not differ significantly for the two groups, indicating that propofol and sufentanil have a similar bradycardic effect. After CPB, the occurrence of tachycardia in the presence of inotropic/chronotropic medications was similar for both groups.

Ischemic Changes

In our study, the propofol-sufentanil group did not have greater ischemia than the sufentanil-midazolam group, despite greater hypotension, lesser intraoperative use of antihypertensive/vasodilator medications with antiischemic effect, the possibility of propofol causing coronary vasodilation that may lead to coronary steal,[25] and the possibility that blood viscosity may have increased after operation due to propofol.[26] Myocardial ischemia occurs more frequently than Holter or TEE monitoring can detect.[27,28] The incidence of ST segment deviation and the incidence of left ventricular wall motion abnormality were less than the incidence of hemodynamic abnormalities as defined in this study. In addition, episodes of ST segment deviation and hemodynamic abnormality were not temporally associated. However, for most of the episodes of ST segment deviation, there was a 5- to 10-beat/min increase in HR from the local baseline to the onset of the episode. The incidence of ST segment deviation was similar to that reported in our other recent study of patients having CABG surgery.[29] If these two anesthetic regimens were suitable in the pre-CPB period of CABG surgery, they are likely to be suitable for patients with CAD undergoing noncardiac surgery.

Study Limitations

The sample size used imposed certain limitations. The number of patients whose Holter ECG data could be evaluated was 142 and 152, for the propofol-sufentanil and sufentanil-midazolam groups, respectively. At $P = 0.05$, this number of patients is sufficient to detect a statistically significant difference of 16% between the incidence of an abnormality in the two groups while maintaining a power of 0.90 ($\beta = 0.10$). Hence this study was not powered to detect differences in the incidence of hard adverse outcomes such as MI and stroke. The incidence of ST segment deviation was used as the primary outcome in this study, although the use of this measure to compare two groups of ambulatory patients is limited by the seemingly random occurrence of ischemic ST segment deviation.[30] Perioperatively, ST segment deviation may not be random, but may occur in response to specific stimuli, as is true of treadmill testing.[31,32] Thus the incidence of ST segment deviation was considered to be a suitable measure of outcome. Because of the many secondary endpoints, a significant difference observed between the two groups for any secondary endpoint is difficult to interpret. The results suggest that clinically important differences in hard adverse outcomes are unlikely between the two groups.

Inadequate *a priori* knowledge of pharmacokinetics and the pharmacodynamics of the various anesthetic agents during CABG surgery precluded their optimal use. Because our aim was to evaluate two clinically useful anesthetic infusion regimens, none of the anesthetic agents was infused by a predetermined protocol, regardless of clinical response, which has substantial variability in the population. Although our approach reduced uniformity in administering the anesthetics to different patients, it is likely to have increased uniformity in the clinical responses of different patients.

Early extubation was not performed during this study because this practice was not routine at the participating clinical sites when the patients were enrolled, from June 1992 to December 1993. Because of this and other changes since then, the issues of cost and length of stay were not addressed.

Conclusions

Target-controlled infusion of propofol supplemented by sufentanil infusion, or target-controlled infusion of sufentanil supplemented by midazolam infusion are suitable for CABG surgery. With the protocol used, episodes of systolic hypertension, hypotension, tachycardia, and bradycardia were common, with hypotension occurring more frequently in the propofol-sufentanil group and hypertension in the sufentanil-midazolam group. However, intraoperative ST segment deviation had a similar prevalence (23% ± 6% *vs.* 24 ± 6%, $P = 0.86$) in the two anesthetic groups and was not temporally associated with episodes of hemodynamic abnormality.

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