

Cardiovascular Responses during Sedation after Coronary Revascularization

Incidence of Myocardial Ischemia and Hemodynamic Episodes with Propofol Versus Midazolam

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Background: Propofol sedation offers advantages for titration and rapid emergence in the critically ill patient, but concern for adverse hemodynamic effects potentially limits its use in these patients. The current study compares the cardiovascular effects of sedation with propofol *versus* midazolam during the first 12 h after coronary revascularization.

Methods: Three hundred fifty-one patients undergoing coronary revascularization were anesthetized using a standardized sufentanil/midazolam regimen, and assigned randomly to 12 h of sedation with either propofol or midazolam while tracheally intubated. The incidence and characteristics of hemodynamic episodes, defined as heart rate less than 60 or greater than 100 beats/min or systolic blood pressure greater than 140 or less than 90 mmHg, were determined using data electronically recorded at 1-min intervals. The presence of myocardial ischemia was determined using continuous three-channel Holter electrocardiography (ECG) and of myocardial

infarctions (MI) using 12-lead ECG (Q wave MI, Minnesota Code) or creatine kinase isoenzymes (CK-MB) analysis (non-Q wave MI, peak CK-MB > 70 ng/ml, or CK-MB > 70 IU/l).

Results: Ninety-three percent of patients in both treatment groups had at least one hemodynamic episode during the period of postoperative sedation. Propofol sedation resulted in a 17% lower incidence of tachycardia (58% *vs.* 70%, propofol *vs.* midazolam; $P = 0.04$), a 28% lower incidence of hypertension (39% *vs.* 54%; $P = 0.02$), and a greater incidence of hypotension (68% *vs.* 51%; $P = 0.01$). Despite these hemodynamic effects, the incidence of myocardial ischemia did not differ between treatment groups (12% propofol *vs.* 13% midazolam; $P = 0.66$), nor did its severity, as measured by ischemic minutes per hour monitored (8.7 ± 5.8 *vs.* 6.2 ± 4.6 min/h, propofol *vs.* midazolam; $P = 0.19$) or ischemic area under the curve (6.8 ± 4.0 *vs.* 5.3 ± 4.2 ; $P = 0.37$). The incidence of cardiac death (one per group), Q wave MI (propofol, $n = 7$; midazolam, $n = 3$; $P = 0.27$), or non Q wave MI (propofol, $n = 16$; midazolam, $n = 18$; $P = 0.81$) did not differ between treatment groups.

Conclusions: Hemodynamic episodes occur frequently in the first 12 h after coronary revascularization. Compared with a standard sedation regimen (midazolam), propofol sedation appears to modulate postoperative hemodynamic responses by reducing the incidence and severity of tachycardia and hypertension and increasing the incidence of hypotension. Both sedation regimens appear similarly safe with respect to myocardial ischemia. These findings indicate that propofol infusion provides effective sedation without deleterious hemodynamic effects in patients recovering from cardiac surgery. (Key words: Anesthetics, intravenous: propofol. Cardiovascular disease: perioperative myocardial ischemia. Intensive care: sedation.)

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herald increased risk for adverse outcomes in patients with coronary artery disease, at significant cost.¹ Most studies of perioperative myocardial infarction (MI) have focused on preoperative or intraoperative ischemia.²⁻⁴ However, recent evidence indicates that the immediate post-CPB period may influence the occurrence of adverse cardiac outcomes.⁵ Sedation regimens, with their potential to modulate the hemodynamic response, assume particular importance during the postoperative period.

The ideal sedation regimen during this critical period of anesthetic emergence minimizes hemodynamic responses to stimulation and facilitates rapid changes in level of consciousness to ensure for rapid awakening and tracheal extubation without increasing the incidence of myocardial ischemia. One of the few studies to examine cardiovascular effects of sedation during the postoperative period showed that providing intense analgesia decreases the severity of myocardial ischemia during the period of infusion.⁶ Prolonged infusions of opioids, however, may significantly delay awakening and extubation, contributing to increased health-care costs.

Previous studies have demonstrated the usefulness of propofol infusions for postoperative sedation in critically ill patients.⁷⁻¹² Unlike the more common regimen of midazolam alone or combined with opioids, propofol neither accumulates nor results in tolerance with repetitive doses or continuous infusions¹³ and decreases the time to extubation once administration is discontinued.^{7,8,11} Compared with midazolam, propofol permits more rapid manipulation of the level of sedation, thereby adjusting sedation to patient condition.¹⁴

Despite these advantages, previous reports of hypotension associated with propofol sedation have limited its acceptance in the cardiac surgical population.^{8,10,12} None of the previous studies of propofol use in the critically ill, however, compared the incidence of myocardial ischemia and hemodynamic consequences of sedation produced by propofol *versus* the more standard regimens, such as midazolam and opioids. Accordingly, in the current study, we compare the cardiovascular effects, including myocardial ischemia, hemodynamic stability, and adverse cardiac outcome, associated with sedation with propofol infusion *versus*

the more frequently used technique of intermittent boluses of morphine and midazolam in the immediate postoperative period in patients recovering from coronary revascularization.

Materials and Methods

Subjects

With informed consent and approval from the appropriate committees on human research, patients scheduled for elective CABG at six university medical centers were enrolled in this prospective, double-blind, open-label, randomized study. Male or female patients older than age 35 yr with at least 50% stenosis of the left main coronary artery or at least 70% stenosis of one or more of the major coronary arteries were eligible for inclusion. Exclusion criteria included: (1) an ejection fraction of <25% before surgery, (2) requiring intraaortic balloon pump therapy, (3) an evolving myocardial infarction (MI), (4) left bundle branch block or permanent ventricular pacemaker, and (5) hemodynamic instability at admission to the intensive care unit (ICU). Hemodynamic stability was defined as a systolic blood pressure of >90 mmHg for 5 min without change in cardiovascular medications and without mechanical ventricular support.

Preoperative and Anesthetic Management

Routine laboratory determinations (including creatine kinase (CK) and CK isoenzymes (CK-MB)) and 12-lead electrocardiogram recording were obtained before surgery. All routine cardiac medications were administered until surgery. Patients were permitted to receive 1-4 mg lorazepam orally on the eve of surgery and were premedicated preoperatively with morphine sulfate (up to 0.2 mg · kg⁻¹) and midazolam (up to 0.1 mg · kg⁻¹) intramuscularly or intravenously.

Anesthesia was induced with sufentanil given by a computer-controlled infusion pump†† set initially for a target effect site concentration (TES) of 3.0 ngm · ml⁻¹.¹⁵ Sufentanil was maintained at the same TES until cardiopulmonary bypass (CPB), at which time the infusion was decreased to a TES of 1.0 ngm · ml⁻¹. At the termination of CPB, the infusion was decreased to a TES of 0.6 ngm · ml⁻¹. Midazolam was continuously infused at 0.5 µg · kg⁻¹ · min⁻¹ throughout the surgical procedure, with increases as needed in increments of 0.1 µg · kg⁻¹ · min⁻¹. If an increase in anesthesia was required, the sufentanil TES was changed in 0.5-1.0

†† The STANPUMP software was written by Steven L. Shafer, M.D., Anesthesiology Service, Palo Alto Veterans Affairs Medical Center, Palo Alto, California.

ngm \cdot ml⁻¹ increments. Vecuronium was administered at induction to facilitate intubation and as required intraoperatively to maintain muscle relaxation. Recovery of neuromuscular function was documented by the presence of four of four twitches on a train-of-four neuromuscular testing before transport to the ICU.

Before CPB, heart rate and blood pressure were controlled to within 20% of baseline measurements as defined as the average of three preoperative readings. Hypertension was treated with increases in anesthesia, followed, if necessary, by an infusion of sodium nitroprusside. Hypotension was treated with a decrease in anesthesia, fluid administration, and/or infusion of phenylephrine. Tachycardia was treated with increases in anesthesia or an infusion of esmolol. Nitroglycerin, by protocol, was not administered prophylactically and was reserved for treatment of increases in pulmonary artery pressure (diastolic \geq 20 mmHg or pulmonary capillary wedge pressure \geq 18 mmHg) or new or worsening myocardial ischemia as detected by ST segment changes, wall motion abnormalities on transesophageal echo, or clinical impression. During CPB, mean arterial pressure was maintained between 40 and 80 mmHg with changes in anesthesia and/or administration of phenylephrine or sodium nitroprusside as necessary. After CPB, the limits for hypertension, hypotension, tachycardia, and bradycardia were 140 mmHg, 90 mmHg, 100 beats/min, and 60 beats/min, respectively, with treatment similar to that of the pre-CPB period. Bradycardia after CPB was treated with temporary pacing.

Postoperative Sedation Period

After surgery, all patients were transported to the ICU and monitored for hemodynamic stability. Hemodynamically stable patients were randomly assigned to sedation with either propofol or midazolam (control). Patients who were hemodynamically unstable were considered to have been screened but not enrolled and were not included in data analyses. After randomization to group, patients were sedated for a minimum of 12 h, measured from release of aortic cross-clamp. Ventilation was controlled to maintain PaO₂ of \geq 100 mmHg and PaCO₂ between 35 and 45 mmHg. After the sedation period, patients were gradually separated from artificial ventilation, and the trachea were extubated per institutional protocol. All concurrent medications administered during the study period were recorded.

Propofol was administered by computer-assisted controlled infusion, initiated at a target plasma con-

centration (TPC) of 0.25 μ g \cdot ml⁻¹. The sedation level was assessed every 15 min for the first hour and then at least hourly thereafter. Increases in the TPC of 0.25–0.5 μ g \cdot ml⁻¹ were mandated to achieve and maintain the target level of 5 on the Ramsay scale (table 1).¹⁶ If a Ramsay level of 5 could not be achieved by adjusting the propofol infusion, sedation was supplemented by intravenous administration of 1–4 mg morphine every 15 min until level 5 was obtained.

In the control group, 1–4 mg midazolam was administered intravenously every 15 min as needed for agitation. If adequate sedation (as determined by the nurse providing patient care) was not achieved within 1 h, 1–4 mg intravenous morphine was administered every 15 min. Morphine and midazolam were continued as necessary throughout the sedation period.

Acceptable limits for heart rate and blood pressure and management of values outside these limits was as defined for the post-CPB period. Bradycardia was treated with temporary pacing.

Hemodynamic Monitoring

Postoperatively, heart rate and blood pressure were continuously recorded electronically at 1-min intervals. Patients for whom hemodynamic data was unavailable for more than 25% of the study period (from ICU entry to 12 h after aortic unclamping) or for whom the start or end of the study period could not be determined were excluded from hemodynamic analysis. Data were analyzed for the presence or absence of hemodynamic episodes during the period of ICU sedation. A hemodynamic episode was defined as an occurrence of tachycardia, bradycardia, hypertension, or hypotension (as defined as for the post-CPB period) that lasted for at least 4 min within any 5-min period. If the same hemodynamic alteration recurred within less than 5 min after a previous episode, it was considered to be

Table 1. Definition of Ramsay Sedation Score

Level	Criteria
1	Patient anxious, agitated, or restless
2	Patient cooperative, oriented, tranquil
3	Patient responds to commands only
4	Patient has brisk response to firm nailbed pressure or other significant stimulus
5	Patient has sluggish response to firm nailbed pressure or other significant stimulus
6	Patient has no response to firm nailbed pressure or other significant stimulus

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a continuation of the same episode. Treatment of a hemodynamic episode was not considered in episode identification.

The presence of a hemodynamic episode was determined initially using validated software algorithms (developed by the Ischemia Research and Education Foundation), with identified episodes validated independently by at least two physicians blinded to treatment group assignment. If they disagreed, the episode was analyzed by a third physician, and the discrepancy was resolved by consensus. Hemodynamic episodes were characterized by incidence, number of episodes per patient, average area under the curve per hour monitored in patients with episodes, and average episode (minutes per hour) monitored in patients with episodes.

Medication Use

The time and route of administration and dose were recorded for all concomitant medications. Cardiac medications were classified as described in appendix 3. Medication use was evaluated by the incidence of use of each class of medication within each sedation group and use of medications across centers. Because hemodynamic stability in either treatment group may have been achieved by an increased use of medications or by the increased manipulation of cardiac medications, the number of medication interventions per patient was analyzed both between groups and across centers. Interventions were defined as the number of bolus doses of medication plus the number of changes in infusion concentration during the sedation period.

Myocardial Ischemia

All patients were monitored continuously using a three-channel Holter ECG recorder (series 8500, Marquette, Milwaukee, WI) for at least 8 h preoperatively, throughout surgery, and for the entire sedation period. The Holter tapes were screened using a Marquette SXP Laser Holter scanner, and episodes of ST segment change consistent with ischemia (≥ 1 mm ST segment deviation from baseline for ≥ 1 min) were identified, characterized, and validated by investigators blinded to treatment group, as previously described.^{2,5,6} Ischemic episodes were characterized by time of onset, duration of ST deviation, and ST deviation-duration integral (area under the curve). Patients whose Holter tapes were unavailable or could not be interpreted were not included in data analysis.

The incidence of ischemia, *i.e.*, the percentage of patients in each treatment group having an ischemic episode starting in a specific period, was determined for each perioperative periods. Periods were defined as: pre-CPB, from initiation of Holter monitoring until beginning of bypass; on CPB, from return of electrical activity on bypass until discharge from the operating room; and ICU on drug, from entry into the ICU until 12 h after aortic unclamping. For each patient, the total duration of ST segment deviation and the area under the curve were divided by the interpretable hours of monitoring obtained during each period to determine the mean and median values for all ischemic patients. If an ischemic episode continued through more than one period, the entire ischemic episode was attributed to the period in which it began.

Cardiac Outcomes

Adverse cardiac outcomes were defined as MI, cardiac death, new or worsened heart failure, or left ventricular dysfunction. Other adverse events considered serious, unexpected, and associated with the use of the drug were recorded in the case report form.

Myocardial infarction was protocol defined as: (1) ECG evidence of infarction based on the Minnesota codes 1.1–1.3 (Q wave MI)^{17,18}; (2) CK-MB isoenzyme concentrations greater than 70 IU/l or ng/ml (non-Q wave MI); or (3) diagnosis of MI made at autopsy, without previously meeting the above Q wave or non-Q wave definitions. A 12-lead ECG was obtained at baseline (within 24 h before surgery), on admission to the ICU, and during postoperative days 1 and 2. Each ECG was reviewed and coded at a central location by two electrocardiographers blinded to treatment group. If either reviewer considered a new perioperative Q wave MI to be definite, probable, or possible, the ECGs for that patient were reviewed by three electrocardiographers, who determined by consensus whether a perioperative Q wave MI had occurred. CK and CK-MB values for diagnosis of non-Q wave MI were determined at each institution before surgery, at entry to the ICU, and every 8 h for 48 h after arrival in the ICU.

Cardiac death was defined as death resulting from a primary cardiac cause, including heart failure, dysrhythmia, MI, or inability to be separated from cardiopulmonary bypass. Congestive heart failure was defined as signs and symptoms of pulmonary congestion accompanied by signs of new or worsening left and/or right ventricular failure and radiologic pulmonary

Table 2. Demographics and Preoperative Characteristics of Patients Receiving Propofol or Midazolam Sedation

	Propofol (n = 154)	Midazolam (n = 158)	P
Gender			
Male	130 (84%)	136 (88%)	0.28
Female	24 (16%)	18 (12%)	
Age (mean \pm SD)	63 \pm 8.5	61 \pm 9.2	0.03
Weight (mean \pm SD)	84 \pm 14.7	85 \pm 16.3	0.5
Body surface area (mean \pm SD)	1.99 \pm 0.20	2.00 \pm 0.21	0.55
Stable angina	111 (72%)	96 (62%)	0.02
Unstable angina	72 (47%)	69 (45%)	0.71
Valvular disease	9 (6%)	10 (7%)	0.91
Hypertension	97 (63%)	87 (56%)	0.22
Prior myocardial infarction	62 (40%)	64 (42%)	0.85
Congestive heart failure	10 (6%)	10 (6%)	0.9
Previous CABG	16 (10%)	5 (3%)	0.01
LV end-diastolic pressure (mean \pm SD)	16.9 \pm 7.3	16.1 \pm 6.65	0.33
Ejection fraction (mean \pm SD)	57.9 \pm 14.0	59.7 \pm 13.6	0.19

CABG = coronary artery bypass graft; LV = left ventricular.

congestion requiring treatment with diuretics. Left ventricular dysfunction was defined as a cardiac index of less than 2 l/min/m² requiring placement of intraaortic balloon pump.

Statistical Methods

Hypotheses using categorical values were adjusted for center and tested with the Cochran-Mantel-Haenszel test. Hypotheses involving continuous variables were subjected to Fisher's F test, with adjustment for center when center was statistically significant. For hemodynamic episodes (table 4), *P* values were determined using the nonparametric median test. All tests were two-sided tests accepting α as 0.05.

Sample Size Calculations. In a study of midazolam sedation in a similar cardiac surgical population, Smith *et al.* reported an incidence of myocardial ischemia of 48% using criteria similar to that of this study.⁵ Sample size calculations were performed to test the hypothesis that propofol produces an incidence of ischemia significantly worse than standard care. Using a one-sided α of 0.05, a 16% increase in the incidence of ischemia could be detected with 90% power with 160 evaluable patients per treatment group. Accordingly, 320 evaluable patients was set as the intended sample size.

Results

Demographic

Three hundred fifty-one patients were enrolled in the study and randomized to treatment group. Because of protocol violation or missing data, 20 patients in the propofol group and 19 in the midazolam group were excluded from analysis, with 154 propofol patients and 158 midazolam patients included.

Clinical and demographic characteristics of the two treatment groups are provided in tables 2 and 3. Patients in the propofol group were older than those in the midazolam group (63 *vs.* 61 yr; *P* = 0.05) and had a higher incidence of prior CABG surgery (10% *vs.* 3%; *P* = 0.05) and stable angina (72% *vs.* 62%; *P* = 0.02). There were no clinically important differences between groups in intraoperative characteristics. Patients in both treatment groups received equivalent amounts of sufentanil or midazolam intraoperatively.

Hemodynamic Alterations

Hemodynamic data were analyzed by group for the incidence and character of hemodynamic episodes occurring in the sedation period. Data from 117 patients given propofol and 150 given midazolam met criteria for inclusion in the hemodynamic analysis. Despite the difference in absolute number of patients, the mean number of monitored hours per patient did not differ between groups. Nearly all patients had at least one hemodynamic episode during the sedation period (93% propofol, 93% midazolam; (fig. 1). However, the incidence of specific hemodynamic episodes differed significantly between groups.

Propofol sedation was associated with a 17% reduction in the incidence of tachycardia (58% *vs.* 70%, propofol *vs.* midazolam; *P* = 0.04) and a 28% reduction in hypertension (39% *vs.* 54%, propofol *vs.* midazolam; *P* = 0.02) but a 33% increase in hypotension (68% *vs.* 51%; *P* = 0.01). Propofol sedation decreased the average number of minutes of tachycardia per hour monitored when compared to midazolam sedation (20 *vs.* 17 min, respectively; *P* = 0.05). Throughout the sedation period, patients with tachycardia spent an average of 20 min of each hour at a heart rate greater than 100 beats/min. Protocol-mandated use of a pacemaker for heart rates less than 60 beats/min reduced the incidence of bradycardia to less than 2% in either group.

The incidence and characteristics of hemodynamic episodes for each of the three postoperative periods

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Table 3. Intraoperative Characteristics of Patients Receiving Propofol or Midazolam Sedation

Variable (mean \pm SD)	Propofol	Midazolam	P
Total operating time (min)	285 \pm 70	286 \pm 63	0.68
Cross-clamp time (min)	55 \pm 21	57 \pm 21	0.29
Bypass time (min)	102 \pm 32	103 \pm 31	0.75
No. of artery/vein grafts	3.2 \pm 0.9	3.4 \pm 1.0	0.04
Total dose of sufentanil (mg)	1.49 \pm 0.48	1.51 \pm 0.57	0.63
Total dose of midazolam (mg)	16.1 \pm 5.0	17.1 \pm 6.0	0.11

Fisher's F test used for comparisons.

are provided in table 4. An individual could be included in analysis for one period but excluded from another, depending on the adequacy of the hemodynamic recording for each period. There were no differences between treatment groups in the incidence of specific episodes in the first hour after ICU entry. Patients in either group who experienced tachycardia in the first hour after ICU entry had an average of nearly 30 min of that hour at heart rates greater than 100 beats/min. As shown in table 4, group-related differences occurred in hours 1–6 and 6–12. Propofol sedation was associated with decreases in the incidence of hypertension and tachycardia and in the number of hypertensive or tachycardiac episodes in hours 6–12. The severity of hypertensive episodes, as determined by hypertensive minutes per hour monitored and area under the curve per hour monitored, was not different between groups in any given period.

Group-related differences in the incidence of hypotension again were apparent in hours 1–6 and 6–12. As with hypertension, the severity of hypotensive episodes was not different between groups in any given period.

Medication Use

Medication use during the postoperative sedation period was similar between groups, despite the differences between groups in the type of hemodynamic episodes (table 5). Propofol sedation was associated with a decrease in the use of opioids and antidysrhythmic agents.

Medications to control tachycardia (β -adrenergic antagonists) were administered infrequently and similarly in the two treatment groups, even though tachycardia occurred frequently and with intergroup differences. Vasodilatory agents were administered to a majority (69%) of patients given propofol despite the increased

incidence of hypotension in this group. The pattern of medication use appeared to be dictated by clinical practice at the study center and not by the occurrence of specific hemodynamic episodes. For example, at centers 1, 3, and 4, fewer than 5% of patients given propofol received β -adrenergic antagonists, compared to 40% of patients receiving propofol at center 2. Use of vasopressor agents also appeared to be related to clinical practice patterns, *i.e.*, fewer than 5% of patients received vasopressors at centers 1 and 5, compared to 58% of the propofol group and 78% of the midazolam group at center 3. Use of nitroglycerin or other nitrates did not differ significantly between treatment groups, but institution-specific differences were again apparent.

The total number of medication interventions per patient was different between treatment groups only at center 1, where patients in the propofol group ($n = 72$) averaged 4.5 interventions per patient *versus* 5.9 interventions per patient in the midazolam group ($n = 68$; $P = 0.01$). None of the drug group by center interactions was statistically significant.

Myocardial Ischemia

The incidence of myocardial ischemia as measured by Holter monitoring was comparable in the two treatment groups during the pre-CPB, post-CPB, and ICU sedation periods (table 6). The two treatment groups also did not differ in the average number of ischemic episodes per ischemic patient, average duration of ischemic events, or minutes of ischemia per hour monitored. The period defined as on CPB had the highest incidence of ischemia, despite being the shortest period, *i.e.*, averaging 2 h compared with 12 h for the pre-CPB and 11 h for the ICU drug on period.

Other Adverse Outcomes

Adverse cardiac outcomes are shown in table 7. Q wave myocardial infarctions occurred in seven patients in the propofol group *vs.* three patients in the midazolam group ($P = 0.27$). One patient in each group experienced a cardiac death. Patients in whom non-Q wave MI was diagnosed by CK-MB mass analysis (ng/ml) are presented separately from those diagnosed using electrophoresis (IU/l; table 7). Although the incidence of non-Q wave MI varied according to the method of CK-MB analysis, there were no significant differences between treatment groups with either method.

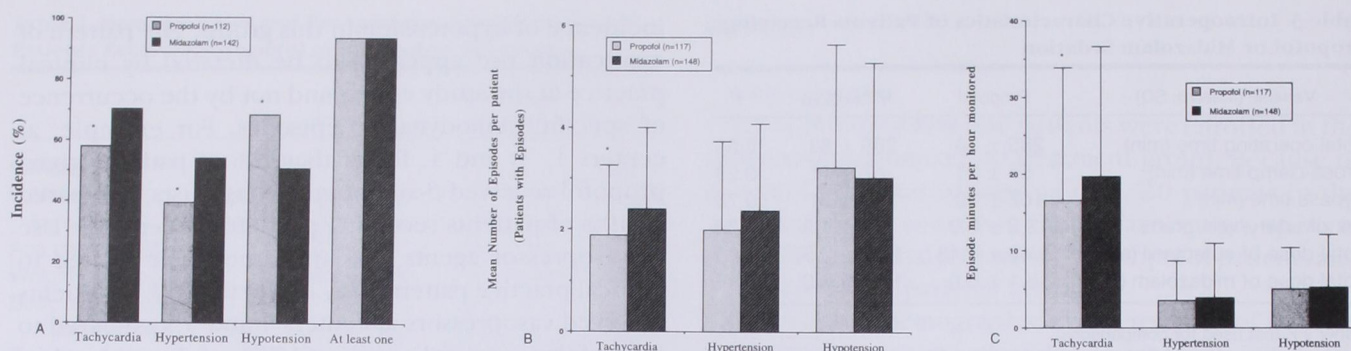


Fig. 1. Hemodynamic events occurring in the period of sedation (intensive care entry to 12 h after aortic unclamping); * $P < 0.05$. (A) Incidence of hemodynamic events by group and type of event. (B) Number of episodes per patient by group and type of event. (C) Average duration of episode (minutes per hour) monitored by group and type of hemodynamic event.

Discussion

Our data demonstrate that postoperative sedation with propofol is not associated with an increase in adverse cardiac events compared to midazolam sedation in patients recovering from coronary revascularization. Furthermore, compared with a standard midazolam sedation regimen, propofol reduced the incidence and severity of tachycardia and hypertension in the 12-h period after surgery, did not exacerbate the incidence or severity of myocardial ischemia or adverse cardiac outcome, and despite increasing the incidence of hypotension, did not result in an increased use of vasoactive agents or an increased number of medication interventions. Additionally, propofol sedation was as-

sociated with a reduction in the amount of supplemental opioid administered.

Despite our use of a protocol mandating rigorous hemodynamic control, including increases in sedation or use of vasoactive agents when hemodynamic parameters were exceeded, there were differences between sedation regimens in both incidence and severity of hemodynamic events. This suggests a true rather than artifactual effect of midazolam and propofol on postoperative hemodynamics.

Previous studies concerned with the relationship between the hemodynamic response to stimulation and its modulation by anesthetic agents have focused on the intraoperative period. To date, the only other study

Table 4. Incidence and Characteristics of Hemodynamic Episodes Occurring in the First Postoperative Hour, in Hours 1–6, and in Hours 6–12 in Patients Receiving Propofol or Midazolam Sedation

	Receiving Drug (hour 0–1)			Receiving Drug (hours 1–6)			Receiving Drug (hours 6–12)		
	Propofol	Midazolam	P	Propofol	Midazolam	P	Propofol	Midazolam	P
Tachycardia									
No. of patients	111	138		109	136		112	134	
Incidence (%)	20.7	19.6	0.82	40.4	57.4	0.01	27.7	38.1	0.09
No. of episodes per patient	1.13 ± 0.34	1.04 ± 0.19	0.23	1.36 ± 0.61	1.69 ± 0.98	0.13	1.39 ± 1.05	1.76 ± 1.01	0.01
Tachycardia min/h monitored	26 ± 20	28 ± 21	0.56	23 ± 17	24 ± 18	0.71	11 ± 15	15 ± 15	0.05
Hypertension									
No. of patients	112	144		116	147		115	146	
Incidence (%)	9.8	17.4	0.09	24.1	38.8	0.01	22.6	28.1	0.32
No. of episodes per patient	1.18 ± 0.4	1.24 ± 0.44	0.7	1.39 ± 0.74	1.39 ± 0.65	0.64	1.5 ± 1.07	2.0 ± 1.22	0.01
Hypertensive min/h monitored	17.6 ± 10.4	15.3 ± 11.3	0.72	23.3 ± 17.5	23.6 ± 18.4	0.71	3.73 ± 3.43	3.7 ± 3.0	0.92
Hypotension									
No. of patients	112	144		116	147		115	146	
Incidence (%)	15.2	9.7	0.18	49	34	0.01	47.8	32.2	0.01
No. of episodes per patient	1.12 ± 0.49	1.14 ± 0.36	0.44	1.96 ± 1.05	1.98 ± 1.3	0.86	2.24 ± 1.58	2.4 ± 1.48	0.3
Hypotensive min/h monitored	15.0 ± 13.8	11.1 ± 8.2	0.58	6.7 ± 5.6	6.1 ± 8.1	0.5	7.3 ± 8.2	9.5 ± 11.2	0.99

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Table 5. Incidence of Use of Medications during the Sedation Period in Patients Receiving Propofol versus Midazolam Sedation

Medication	Propofol (n = 149)	Midazolam (n = 150)	P*
Opioid	74 (49.3)	119 (79.9)	<0.001
Antihypertensive	109 (72.7)	119 (79.9)	0.19
β-adrenergic antagonist	10 (6.7)	16 (10.7)	0.3
Calcium channel antagonist	9 (6.0)	10 (6.7)	0.99
Vasodilator	104 (69.3)	113 (75.8)	0.26
Anti-ischemia (nitrates)	42 (28)	40 (26.8)	0.93
Cardiac stimulant	109 (72.7)	95 (63.7)	0.13
Inotropic agent	95 (63.3)	82 (55)	0.18
Vasopressor	32 (21.3)	31 (20.8)	1.00
Antidysrhythmic	12 (8)	26 (17.5)	0.02

Values are no. (%) of patients.

* Continuity adjusted chi-square.

to focus on the postoperative period has demonstrated that combining a standard sedation regimen (e.g., midazolam) with a constant infusion of opioid decreases the severity but not the incidence of postoperative myocardial ischemia and does not alter the incidence of hemodynamic episodes.⁶ Hemodynamic events were present in more than 93% of our patients during the first 12 h postoperatively.

Studies regarding the hemodynamic effects of propofol in the postoperative period appear to conflict: Some studies demonstrate no hemodynamic effect of sedative doses,^{7,9,11} and others show a decrease in blood pressure relative to other anesthetic or sedation regimens.^{8,10,12} Although our data support an increased incidence of hypotension associated with propofol sedation, the duration and severity of hypotensive epi-

Table 7. Incidence of Adverse Clinical Outcomes in Patients Receiving Propofol versus Midazolam Sedation

Variable	Propofol	Midazolam	P
Q-wave myocardial infarction	7 (5)	3 (2)	0.27
Cardiac death	1	1	
Unstable angina	0	0	
Congestive heart failure	0	0	
LV dysfunction	1	0	
Distribution of CK-MB peak value IU/L	n = 59	n = 60	
Incidence of CK-MB > 50	21 (36)	20 (33)	0.85
Incidence of CK-MB > 70	10 (17)	12 (20)	0.81
ng/ml	n = 95	n = 94	
Incidence of CK-MB > 50	11 (12)	15 (16)	0.41
Incidence of CK-MB > 70	6 (6)	6 (6)	1.00

Values are no. (%) of patients.

sodes appeared to be mild and were not associated with deleterious effects.

Despite continuous sedation and protocol-mandated treatment of hemodynamic episodes, the incidence of tachycardia (65%) and the mean number of minutes of tachycardia per hour (20 min) were high in the entire study population. This finding in postoperative cardiac surgical patients is disturbing and suggests a potential risk to this population, because earlier studies indicate that tachycardia is associated with adverse cardiac outcomes.^{4,5,19,20} These studies have shown that (1) tachycardia is frequent and persists throughout the postoperative period,^{5,21} (2) patients with myocardial ischemia are more likely to experience tachycardia than hypotension or hypertension,^{4,5} and (3) a temporal relationship often exists between the occurrence of myocardial ischemia and hemodynamic episodes (e.g., in

Table 6. Incidence and Characteristics of Ischemic Episodes during Propofol versus Midazolam Sedation

	Preoperative to On Bypass Period			On CPB to ICU Entry Period			ICU "On Drug" Period		
	Propofol	Midazolam	P	Propofol	Midazolam	P	Propofol	Midazolam	P
No. of patients	126	119		127	123		121	121	
Hours monitored*	21.6 ± 3.8	19.3 ± 1.2	0.52	2.4 ± 0.8	2.5 ± 0.7	0.57	10.9 ± 2.6	11.4 ± 2.0	0.12
Incidence (%)	20	19	1	21	16	0.34	12	13	0.66
Ischemia min/h*									
Mean	3.6 ± 4.5	3.1 ± 2.8	0.68	44.5 ± 77.6	23.9 ± 21.2	0.2	8.7 ± 5.8	6.2 ± 4.6	0.19
Median	2.4	2.4	0.87	19.8	14	0.44	7.2	6.1	0.19
AUC/h*									
Mean	3.8 ± 7.0	2.7 ± 2.9	0.48	36.3 ± 60.7	16.2 ± 12.9	0.11	6.8 ± 4.0	5.3 ± 4.7	0.37
Median	2.1	1.8	0.92	18.7	11.5	0.42	6.5	4.2	0.37

* Hours of interpretable time.

two different studies, 61%⁴ and 41%,² respectively, of the ischemic episodes were associated with hemodynamic episodes). Although many episodes of myocardial ischemia are due to vasoactive, not hemodynamic, mechanisms,^{2,4,5,20} Smith *et al.* found a relationship between myocardial ischemia and persistently elevated postoperative heart rate.⁵ In a study of 50 patients monitored for 10 days after CABG surgery, they found that 10% experienced adverse cardiac outcomes, all of which occurred on the day of surgery, were preceded by early postoperative ischemia, and were associated with elevated heart rate.

Use of medications that decrease heart rate (*e.g.*, β -adrenergic antagonists) has been shown to reduce the incidence and sequelae of myocardial ischemia in different patient populations. Slogoff and Keats have demonstrated that treatment with β -blocking agents is more effective than calcium channel antagonists in reducing the incidence of pre-CPB myocardial ischemia.²² β -Adrenergic antagonist therapy has been shown repeatedly to be effective in reducing mortality in a different setting of myocardial ischemia, namely, acute myocardial infarction.²³⁻²⁵ However, the use of this therapy by our clinical investigators was low (9% overall). One study found that the use of β antagonists is inappropriately low in patients sustaining an acute myocardial infarction and in elderly patients at risk for cardiac morbidity, despite clear evidence of beneficial effect.²⁶⁻²⁸ Despite our concerns regarding the incidence of tachycardia in this study, the association between tachycardia and myocardial infarction in the revascularized heart is not clear. Further studies should be undertaken to investigate the efficacy of β -adrenergic blockade in the post-CPB cardiac surgical population and to determine its effect(s) on the incidence of myocardial ischemia or adverse cardiac outcomes.

In the current study, myocardial ischemia (as defined by Holter ECG monitoring) was detected in only 12–13% of patients in either group during the period of ICU sedation. These incidences are less than those reported previously (40–50%).^{2,5} This difference may be related either to the protocol-mandated intense sedation and treatment of hemodynamic episodes or to differences in monitoring duration. The incidence of ischemia will vary directly with the duration of monitoring, *e.g.*, our postoperative monitoring period lasted 12 h, compared with 2 or 7 days^{2,5} in other studies reporting a greater incidence of ischemia.

The incidence of significant adverse cardiac outcome in our patients, *i.e.*, a 2–4% incidence of myocardial infarction and two cardiac deaths, is similar to that reported previously.^{5,6} Other adverse outcomes of congestive heart failure or ventricular dysfunction were comparably rare in the two treatment groups. There was a low, comparable incidence of other adverse outcomes in both sedation groups.

Limitations of This Study

Because of the complexity of the data and the time frame over which it was acquired, it was not possible to synchronize all of the data collection tools. Consequently, the onset and offset of ischemic episodes could not be related specifically to hemodynamic episodes. Additionally, our sample size was predicated on previous reports of myocardial ischemia using monitoring periods longer than 12 h. This study was designed to detect a 16% increase in myocardial ischemia associated with propofol sedation. The low incidence of myocardial ischemia we detected suggests that our study is adequately powered to detect a doubling of the incidence of myocardial ischemia (one-tailed α 0.05; power 80%) but underpowered to detect smaller increases in ischemia. Similarly, the low incidence of death or MI also results in a study underpowered to show a group difference in either outcome.

Sedation was administered differently in the two groups. Because sedation with propofol was a form of treatment unfamiliar to most of the ICU staff at the participating study centers, care was taken to provide clear guidelines for propofol administration (Ramsay scores). However, the use of midazolam was not guided because it has been the standard of care at the participating centers. In addition, infusions of midazolam were uncommon at the participating centers, and therefore, bolus injections were permitted for midazolam. These differences in administration of sedation may account for some of the differences between treatment groups in the incidence and severity of hemodynamic events.

Finally, an interesting control group was not included in this study. With increasing financial constraints limiting the duration of the ICU stay postoperatively, many CABG patients are extubated within 4 h of surgery. Previous reports that the incidence of myocardial ischemia is the greatest in the first 12 h after cardiac surgery raise concerns that rapid awakening and extubation may increase the hemodynamic events in this period, con-

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tributing to morbidity and mortality. Alternatively, early extubation may be associated with decreases in myocardial ischemia and adverse events. Further studies should be undertaken to investigate the benefits and hazards of early awakening *versus* more prolonged sedation in this population.

In summary, compared with a standard midazolam sedation regimen, the use of propofol for sedation in the 12-h period after CABG surgery results in a decrease in the incidence and severity of tachycardia, a decrease in the incidence of hypertension, and an increase in the incidence of hypotension. Despite these hemodynamic differences, the incidence of myocardial ischemia was not different between the treatment groups. These findings indicate that propofol infusion provides effective sedation without deleterious hemodynamic effects in patients recovering from cardiac surgery.

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Appendix 3. Medications**Analgesic**

Analgesic: aspirin, acetaminophen, Ketorolac
Narcotic: morphine, meperidine

Antihypertensive

β -antagonist: labetalol, esmolol, propranolol, metoprolol
Calcium channel antagonist: diltiazem, nifedipine, verapamil
Vasodilator: sodium nitroprusside, trimethoprim, regitine,
amrinone, milrinone

Anti-ischemia

Nitrate: nitroglycerin (paste or infusion)

Cardiac stimulant

Inotrope: dopamine, dobutamine, epinephrine, digoxin,
calcium, isoproterenol
Vasopressor: phenylephrine, norepinephrine

Antiarrhythmic

Lidocaine, procainamide