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The Role of an Ultra Short-acting Adrenergic Blocker (Esmolol) in Patients Undergoing Coronary Artery Bypass Surgery

LAWRENCE HARRISON, M.D.,* FIONA E. RALLEY, M.B.CH.B.,† J. EARL WYNANDS, M.D.,‡
G. ROSS ROBBINS, M.D.,† MAGDI SAMI, M.D.,§ RUTH RIPLEY, R.N.,¶ HEATHER A. FULLERTON**

Despite advances in anesthetic techniques, the reported incidence of prebypass myocardial ischemia is 37–50%.[1,2] Both tachycardia and hypertension, which have been shown to be undesirable in patients with coronary artery disease,[3,4] may be due to inadequate beta blockade during narcotic-O_2 anesthesia.[5]

Propranolol has been used during the prebypass period to modify these responses.[6] However, any undesirable effects may be persistent because of its elimination half-life of 100 min.

Esmolol, a new intravenous beta$_1$ adrenergic antagonist, has a rapid onset and short duration of action ($tl/2_B$ = 9 mins.). Its effect on heart rate was absent 5 min after cessation of an infusion, and plasma levels of esmolol were undetectable 15 min after termination of the infusion.[7] Tachycardia, in response to elevated endogenous norepinephine plasma concentrations, has been attenuated by esmolol in patients during induction of anesthesia for coronary artery surgery.[7]

The purpose of this study was twofold. First, we wished to determine if esmolol would reduce the incidence of prebypass myocardial ischemia and arrhythmias in patients undergoing coronary bypass surgery, anesthetized with fentanyl-O_2. Second, we sought to determine if the use of esmolol altered the requirements for additional volatile anesthetic agents.

METHODS

With Ethics Committee approval and informed consent, thirty patients scheduled for elective myocardial revascularization were studied. Table 1 lists the exclusion criteria for admission to the study. Patients were maintained on their routine medication until the evening prior to surgery, and beta-adrenergic blocking drugs, calcium channel blocking drugs, and nitrates were continued up to the time of premedication, as is our standard practice. All patients received morphine (0.15 $mg \cdot kg^{-1}$) im and scopolamine (0.005 $mg \cdot kg^{-1}$) im 60–90 min preoperatively.

Thirty minutes before transfer to the operating suite, a continuous ECG recording monitor (Holter) was fitted to each patient using a dual electrocardiographic battery operated Reynolds Tracker II™ cassette recorder.[8] After appropriate skin preparation, the positive electrodes were placed on the 6th rib at the mid-axillary line for ch_1 and on the same transverse plane approximately 1.5 cm to the left of the spinal column for ch_2, to obtain modified leads V_6 and V_9, respectively. The two negative electrodes were positioned on the right shoulder posteriorly. The choice of electrode placement was designed so as to detect left ventricular ischemia without encroaching on the surgical field.

Upon arrival in the operating room, catheters were inserted, under local anesthesia, into a peripheral vein, a radial artery, and the pulmonary artery. Following a stabilization period of 15 min, a hemodynamic profile was recorded. This included the direct measurements heart rate (HR), systemic systolic and di-astolic blood pressure (SBP, DBP), central venous pressure (CVP), pulmonary artery systolic and diastolic pressures (SPAP, DPAP), and mean pulmonary artery occlusion pressures (PCWP). Derived values were calculated, using standard formulae, for mean arterial pressure (MAP), mean pulmonary arterial pressure (MPAP), cardiac index (CI), systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), stroke work index (SI), left ventricular stroke work (LVSW), left ventricular stroke work index (LVSWI), right ventricular stroke work (RVSW), right ventricular stroke work index (RVSWI), rate-pressure product (RPP), and triple index (TI). Cardiac output (CO), measured by thermodilution, was taken as the average of three consecutive recordings.

The patients were randomized to receive, in a double-blind fashion, either an infusion of esmolol diluted in a 1:25 solution using 5% dextrose (Group E) or an infu-

* Senior Resident in Anesthesia.
† Assistant Professor in Anesthesia.
‡ Professor in Anesthesia and Surgery.
§ Assistant Professor in Cardiology.
¶ Research Assistant in Cardiology.
** Research Assistant in Anesthesia.

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Address correspondence to Dr. Ralley: Department of Anaesthesia, Royal Victoria Hospital, 687 Pine Avenue West, Montreal, Quebec, H3A 1A1. (No reprints available.)

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TABLE 1. Exclusion Criteria

Pregnancy
Atrial flutter or atrial fibrillation
Atrio-ventricular conduction block greater than first degree
Conditions that preclude treatment with beta-adrenergic blocker; *e.g.*, congestive heart failure, bronchial asthma, etc.
Myocardial infarction within the previous 3 months
Severe hepatic or renal disease
Systolic blood pressure less than 100 mmHg or cardiogenic shock
Severe electrolyte imbalance
Adrenergic augmenting drugs, *e.g.*, MAO inhibitors, or adrenergic depleting drugs, *e.g.*, reserpine
Long-term beta-adrenergic blocking drugs, *e.g.*, nadolol
Calcium channel antagonists other than nifedipine

sion of 5% dextrose alone (Group C). The infusion was started with a loading dose of 500 mcg $\cdot$ kg^{-1} $\cdot$ min^{-1} for 4 min, followed by a maintenance infusion of 300 mcg $\cdot$ kg^{-1} $\cdot$ min^{-1}, continued until the start of bypass. This dose has been shown to be effective in preventing isoproterenol-induced tachycardia in normal volunteers.[9] Induction of anesthesia began 10 min after the start of this infusion, using a loading dose of fentanyl 40 mcg $\cdot$ kg^{-1} at a rate of 500 mcg $\cdot$ min^{-1}, followed by a constant infusion of 0.4 mcg $\cdot$ kg^{-1} $\cdot$ min^{-1} until approximately 10 min prior to the start of cardiopulmonary bypass (CPB). Muscle relaxation was produced with pancuronium (0.15 mg $\cdot$ kg^{-1}), and isoflurane was administered for the treatment of hypertension (*i.e.*, SBP > 20% above control value), as required. The inspired concentration of isoflurane was carefully recorded on a minute-to-minute basis. Further hemodynamic profiles were recorded prior to the start of induction, immediately post-intubation, and 1 min after the start of skin incision, sternotomy, and aortic dissection. HR, SBP, and DBP were also recorded at 1 min intervals for 5 min from the start of the infusion, and after each hemodynamic profile. Total dose of drug infused, the time from induction to the start of bypass, and the time on bypass was also recorded.

The Holter recordings were analysed using a Reynolds Pathfinder™ analyzer and trend system fitted with a Reynolds Replay II playback.[10] Both recording channels were calibrated with a square wave of 10 mm/mV. The tapes were evaluated both qualitatively and quantitatively for ST segment shifts, and both HR and ST trends, as well as representative strips, were obtained. Because esmolol has been shown to have antiarrhythmic activity,[11] in addition, ventricular arrhythmias were also quantified. The ST trends and ECG strips were evaluated for myocardial ischemia independently by a cardiologist who had no knowledge of the patient's treatment group. An ischemic episode was defined as a period of ST segment elevation or depression greater than 1 mm from baseline recordings in at least one channel of the Holter recording. Periodic checks of the PCWP waveform were made for significant a or v waves during the prebypass period as a further method of detecting early myocardial ischemia.[12] A preoperative Holter monitor ECG strip was compared to the ward control ECG in each patient to detect any new ischemic episodes present on arrival in the OR.

The hemodynamic mean values are presented with the standard error of the mean (SEM) as an index of dispersion. The change in HR and SBP was calculated as a percentage of the baseline value. Analysis of variance for repeated measurements was performed on the changes in hemodynamic observations. This analysis included the patient as the random blocking factor and tested for significant differences between treatments, significant differences among events, and significant interactions between treatment and event. Testing for treatment differences at each event was performed using least mean squares.††

The incidence of prebypass ischemia and the occurrence of significant arrhythmias in each group was compared using chi-squared analysis with Yates correction for continuity. The amount of isoflurane administered to each patient was expressed as the product of inspired concentration and time in minutes during which that concentration was administered. The $\log_e$ doses received were compared using the Student's t test. In all analyses, the null hypothesis was rejected when $P < 0.05$.

RESULTS

Comparison of the demographic data is shown in table 2. There were no significant differences between the groups. Important hemodynamic data, both measured and derived at the various time intervals during the study, are shown in tables 3 and 4. There were significant changes within groups when comparisons were made between event and baseline in SBP, HR, RPP, CI, PCWP, CVP, PVR, LVSWI, and SV, and between event to previous event in HR, RPP, CI, and SVR ($P < 0.05$). When comparisons were made, using least mean squares, for treatment differences at each event, significant differences between treatment groups were found for the change in HR at sternotomy only with percentage change from baseline (fig. 1). In both groups, the HR rose significantly at induction, compared with baseline values, the maximal increase from baseline occurring at intubation (27% in the control group and 25% in the esmolol group). Thereafter, they fell to post-induction level by the time of skin incision, but remained above baseline values throughout the prebypass period (table 3). Significant differences in

†† Searle SR, Speed FM, Milliken GA: Population marginal means in the linear model: An alternative to least squares means. Am Statistics 34:216–221, 1980

TABLE 2. Demographic Data*

	Age (yr)	Weight (Kg)	Height (cm)	Sex	Preop BP (mmHg)	N. Y. H. A. Class	XCT (mins)	BPT (mins)	No. Grafts/Patient
Group E	56.7 ± 2.06	75.20 ± 2.25	170.33 ± 1.47	M 13 F 2	Syst 129.0 ± 4.4 Dias 81.0 ± 2.9	III/IV 15 IV/IV 0	46.60 ± 4.87	84.73 ± 7.27	3.1 ± 0.3
Group C	56.0 ± 2.16	76.99 ± 3.42	172.33 ± 1.63	M 14 F 1	Syst 129.0 ± 4.7 Dias 76.3 ± 3.3	III/IV 14 IV/IV 1	51.07 ± 3.96	98.26 ± 8.20	3.5 ± 0.3

XCT = Cross clamp time during CPB; BPT = Total bypass time; N. Y. H. A. = New York Heart Association; M = Males; F = Females.

* Mean values ± SEM.

TABLE 3. Hemodynamic Data I*

		Baseline	Preinduction	Preintubation	Intubation	Skin Incision	Sternotomy	Aortic Dissection	Prebypass
HR (bpm)	E	54.4 ± 2.1	52.3 ± 1.8	62.3 ± 1.9†‡	66.8 ± 2.5†	61.8 ± 1.8†	62.1 ± 2.0†	61.3 ± 1.9†	64.5 ± 2.0†
	C	50.5 ± 1.4	50.5 ± 1.4	55.8 ± 1.6†‡	64.3 ± 2.2†	58.3 ± 2.1†	61.9 ± 1.6†	59.3 ± 2.4†	64.3 ± 2.8†
SBP (mmHg)	E	145.5 ± 6.0	136.4 ± 5.4	137.7 ± 6.8	134.6 ± 3.3	126.5 ± 2.7†	127.9 ± 3.8†	120.7 ± 3.0†	110.5 ± 2.7†
	C	134.5 ± 5.8	135.1 ± 5.3	133.6 ± 6.5	134.3 ± 7.0	127.3 ± 4.3	136.1 ± 6.2	123.8 ± 3.1	110.1 ± 3.0
RPP	E	7.9 ± 0.5	7.1 ± 0.3†‡	8.6 ± 0.5‡	9.0 ± 0.5†	7.8 ± 0.3	7.9 ± 0.3	7.4 ± 0.3	7.2 ± 0.4
	C	6.8 ± 0.3	6.8 ± 0.3	7.5 ± 0.4	8.7 ± 0.4†‡	7.4 ± 0.3	8.4 ± 0.4	7.4 ± 0.4	7.1 ± 0.3

bpm = beats · min^{-1}; E = Esmolol group; C = Control group.
* Mean values ± SEM.
† $P < 0.05$ from baseline.
‡ $P < 0.05$ from previous recording.

percentage change in SBP from baseline values were found between groups at preinduction, skin incision, and all events from sternotomy to 5 min after the start of aortic dissection (fig. 2). Mean SBP decreased in the esmolol group from skin incision until the start of CPB, falling to 78% of baseline values. In the control group, mean SBP was virtually unchanged until aortic dissection, and then fell to 84% of baseline value by the start of CPB (fig. 2). The rise in SBP seen in the control group at sternotomy matched the increase in HR, which also occurred at this time. These increases were not seen in the esmolol group.

There were no significant differences between treatment groups for any of the other hemodynamic variables measured. During the prebypass period, there was no significant change in PCWP in the esmolol group, although the PCWP dropped significantly compared with baseline values in the control group from skin incision to the start

TABLE 4. Hemodynamic Data II

		Baseline	Pre-induction	Intubation	Skin Incision	Sternotomy	Aortic Dissection
Cardiac Index (l · min^{-1} · m^{-2})	E	2.62 ± 0.09	2.46 ± 0.08	2.82 ± 0.14†	2.58 ± 0.17	2.44 ± 0.13	2.37 ± 0.11
	C	2.50 ± 0.06	2.36 ± 0.09	2.99 ± 0.16*†	2.67 ± 0.19	2.65 ± 0.23	2.32 ± 0.19
PCWP (mmHg)	E	13.27 ± 1.2	14.27 ± 1.1	13.6 ± 1.5	11.53 ± 0.9	10.87 ± 0.9	10.60 ± 1.3
	C	14.07 ± 0.8	14.67 ± 1.1	12.9 ± 2.0	11.13 ± 1.0*	10.40 ± 0.9*	10.07 ± 0.9*
CVP (mmHg)	E	8.13 ± 1.0	9.0 ± 1.2	8.5 ± 0.8	7.9 ± 0.9	7.0 ± 0.6	5.6 ± 0.8*
	C	9.6 ± 0.9	9.5 ± 0.9	8.3 ± 0.9	8.4 ± 0.6	7.3 ± 0.7*	7.2 ± 0.7*
SVR (dys · s · cm^{-5})	E	1462 ± 64	1499 ± 59	1351 ± 71	1476 ± 90	1570 ± 85	1520 ± 70
	C	1372 ± 72	1517 ± 88	1242 ± 93†	1350 ± 112	1520 ± 158	1659 ± 157
PVR (dys · s · cm^{-5})	E	100 ± 12	98 ± 11	92 ± 6	91 ± 10	92 ± 12	109 ± 12
	C	124 ± 8	113 ± 12	119 ± 14	89 ± 8*	96 ± 12	115 ± 13
LVSWI (gm · m · m^{-2})	E	55.71 ± 3.8	52.49 ± 3.8	47.43 ± 3.2	46.73 ± 3.2	44.24 ± 3.4*	41.15 ± 2.3*
	C	51.84 ± 3.3	50.36 ± 3.5	50.91 ± 3.1	48.93 ± 4.0	47.69 ± 3.6	43.13 ± 3.2
SV (mls)	E	91.9 ± 4.7	89.5 ± 4.8	79.2 ± 3.3*	78.6 ± 4.9*	73.9 ± 4.1*	72.9 ± 3.6*
	C	94.7 ± 4.2	89.9 ± 5.2	88.2 ± 3.9	87.3 ± 5.5	80.6 ± 5.9	76.3 ± 6.7*

Mean values ± SEM.
E = Esmolol group; C = Control group.
* $P < 0.05$ from baseline.
† $P < 0.05$ from previous recording.

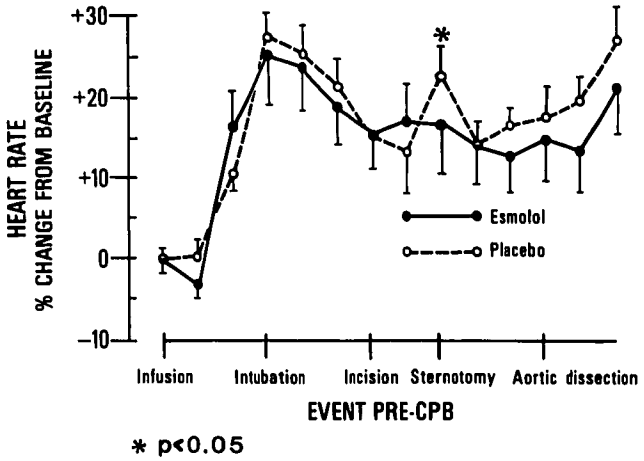

FIG. 1. The percentage change in HR compared to baseline value. *$P < 0.05$ between groups.

of CPB. Similarly, there was little change seen in the CVP in the esmolol group until aortic dissection, when it decreased significantly. In the control group, changes in the CVP tended to follow changes in the PCWP, and were significantly lower than baseline measurements from sternotomy to the start of CPB.

Four patients (13.3%) developed ischemia during the prebypass period. Three patients were in the control group, and one was in the esmolol group. The periods of ischemia ranged from 15 s to 5 min. Two of these four patients required cardiac support to wean from bypass (with ischemia times of 15 s and 5 min, respectively), and one of the two required insertion of an intraaortic counterpulsation balloon. Five of the remaining 26 patients with no prebypass ischemia required inotropic support at

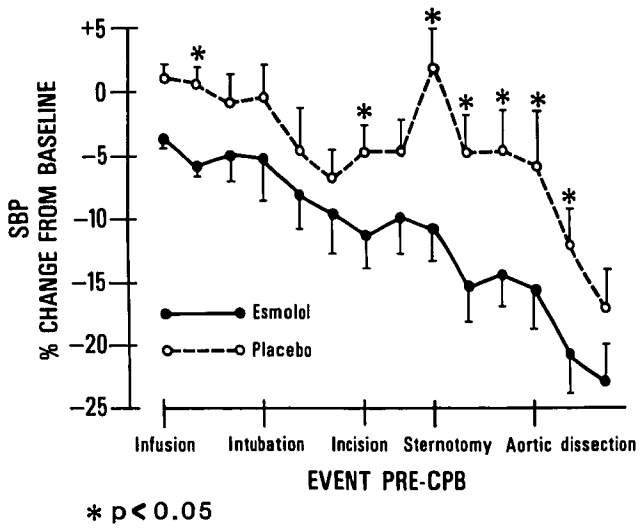

FIG. 2. The percentage change in SBP compared to baseline value. *$P < 0.05$ between group.

TABLE 5. Requirement for Additional Volatile Agents

		All Patients	Non Hypertensives
Group C	n	11/15	8/15
	Min	31.93 ± 5.8	31.53 ± 5.6
	Log_e	8.42 ± 0.2	8.27 ± 0.2
Group E	n	11/15	8/15
	Min	16.41 ± 5.6	8.25 ± 1.4
	Log_e	2.32 ± 0.3	1.96 ± 0.2
		$0.02 < P < 0.01$	$P < 0.01$

Mean values ± SEM.
Min = minutes at 1% concentration of isoflurane.

termination of CPB. All recorded episodes of ischemia occurred around the time of aortic dissection and cannulation. The incidence of "complex ventricular arrhythmias" that occurred during this period was 73.3% in the control group and 26.7% in the esmolol group ($P < 0.05$).

Eleven patients in each group required additional volatile anesthetic. The total amount received as measured by the number of minutes of 1% inspired concentration of isoflurane was significantly less in the esmolol group (table 5). When all patients who required additional volatile anesthetic to lower their SBP for aortic cannulation were also removed (three from each group), the difference becomes even more significant ($P < 0.02$). There was no significant difference between the two groups in the mean time of the infusion or the amount of solution infused.

DISCUSSION

Despite anesthetic techniques designed to maintain hemodynamic stability during the prebypass period, recent studies[1,2] continue to show the incidence of myocardial ischemic episodes during this time to range from 37–50%. The incidence of 13% (20% in the control group and 6.7% in the esmolol group) in our study is lower than those reported in other studies. Although the incidence of 6.7% in the esmolol group was not significantly different from control, perhaps due to the small number of patients in each group (Type 2 statistical error), to our knowledge, it is the lowest reported incidence of prebypass ischemia detected by Holter monitoring in patients undergoing CABG surgery. We believe that significant factors in this low incidence (13%) of prebypass ischemia are the preoperative management and preparation of the patient, the anesthetic technique used, and, probably, the intraoperative use of an infusion of a short acting beta adrenergic blocking drug.

We use a standard premedication of morphine and scopolamine, which produces a well-sedated and cooperative patient prior to induction of anesthesia. De Lange *et al.* showed a marked reduction in cardiovascular response in patients in whom beta adrenergic blocking drugs

were continued up to the day of surgery.[5] Our practice is also to continue beta blockers, calcium channel blockers, and nitrates up to the time of premedication, which is in contrast to Thomson's study,[2] where beta blockade therapy was discontinued the evening prior to surgery, while, in Slogoff's study,[1] the decision to continue beta blockade therapy up to the day of surgery was not consistent. Therefore, it is possible that there was not a clinically significant degree of beta blockade present in some of their patients at the time of surgery. None of our patients developed new ischemic changes prior to induction of anesthesia, when their Holter baseline tapes were compared to their ward control ECG. This is in contrast to Slogoff's findings of an incidence of 50% of new changes in those patients who subsequently developed further prebypass ischemia.

The anesthetic technique used in this study of fentanyl–O_2 characteristically produces a slow heart rate at induction. Therefore, despite the transient increase in heart rate seen at induction and intubation, the HRs during the study remained in a range considered favorable for patients with ischemic heart disease.[3] This may explain the observation that the periods of recorded ischemia in our patients were not related to periods of hemodynamic instability seen at induction and intubation, but rather to a period when surgical stimulation or complications (*e.g.*, bleeding during atrial cannulation) may contribute significantly to the incidence of prebypass ischemia. In Slogoff's study, 40% of the patients who developed tachycardia (defined as a HR > 100 bpm) had associated ischemia. The maximum increase in HR in our study was seen during intubation, 25% from baseline value in the esmolol group, and 27% in the control group (fig. 1). However, the absolute values, a rise from 50 bpm to 64 bpm, makes this change of little clinical significance. As has been reported previously,[13] we also noted a rise in heart rate starting at induction of anesthesia in both groups. This was attributed to the use of pancuronium, but there was no period of ischemia seen on the Holter tapes at this time. Thomson *et al.*[13] postulated that, by delaying the administration of the pancuronium from the administration of the fentanyl, one might separate the potential synergistic effect of these two drugs on the sympathetic nervous system. We attempted to reduce this possible cause of tachycardia by administering the pancuronium in small increments over the 4–5 min induction period.

It is likely that the degree of beta blockade present in our patients during the prebypass period was a major contributing factor for both the lower incidence of ischemia and the minor differences between the two groups. Sill *et al.* concluded that the plasma concentration of propranolol was a major factor influencing hemodynamic responsiveness in patients undergoing coronary artery surgery.[14] Twenty-nine of the 30 patients studied were receiving beta adrenergic blocking drugs up to 2 h prior to the start of surgery. The one patient in our study not on chronic beta blocker therapy preoperatively was randomized to receive esmolol, and had a smooth prebypass period. Our findings are in agreement with the results found by Menkhaus *et al.*[7] Although they claimed that esmolol attenuated the HR response to induction and intubation, there was a 23% increase in HR from baseline values in all three of their esmolol treatment groups, which is similar to our finding of a 25% increase in the esmolol group.

The average prebypass time in our study was 90.3 min. It might be postulated that, by this time, there is a reduction in the therapeutic effect of the preoperative beta blockers given preoperatively in the control group, compared to the maintenance of an effective therapeutic plasma level in the esmolol group. This dissipation in beta blockade activity may account for the difference seen in the occurrence of "complex ventricular arrhythmias," with a marked reduction in the esmolol group. A further explanation for this reduction may be due to the antiarrhythmic properties that have been demonstrated by esmolol.[11] It might be speculated that the addition of an infusion of a beta blocker during the prebypass period attenuated the ventricular response to catecholamines, and so significantly reduced the incidence of arrhythmias observed in the control group.

Narcotic requirement in patients on chronic preoperative beta adrenergic blocking drugs has been shown to be reduced,[15] as manifested by the reduction in the incidence of hypertension associated with noxious stimuli in the prebypass period.[5] Eleven patients in each group required additional volatile anesthetic, but the average total amount was significantly less in the patients receiving the esmolol infusion. Three patients in each group required additional volatile anesthetic, only to reduce their SBP below a mean of 100 mmHg at the time of aortic cannulation at the request of the surgeons. When these patients are removed from each group, the requirement for additional volatile agents remains virtually unchanged in the control group, in marked contrast to the esmolol group, where there is a further reduction of almost 50% (table 5). The mechanism of action here, whether potentiation or blunting of responses, is unclear. It has been suggested that possible mechanisms may include changes in CNS opiate receptor activity, decreases in drug distribution, plasma volume or metabolism, or changes that influence the opiate transfer across the blood-brain barrier.[15,16]

Girard *et al.*[17] studied 20 patients undergoing CABG anesthetized with comparable doses of fentanyl and given esmolol in a manner similar to the patients in our study. However, they withheld the morning dose of beta adrenergic and calcium channel blocking drugs, while our pa-

tients were maintained on these drugs to the time of surgery. In contrast to our results, patients receiving esmolol had significantly less tachycardia at intubation than did the control patients. The mean HR in their esmolol group was 67 bpm, similar to the HR of the esmolol group in this study. The greater increase in HR in their placebo group compared to ours probably reflects differences in preoperative drug regimens for heart rate control. In addition, our study describes the incidence of ischemia obtained by Holter monitoring, and suggests that patients given esmolol have significantly fewer ventricular arrhythmias and decreased requirements for additional volatile anesthetic drugs.

In conclusion, we found esmolol to be a safe drug for use in patients undergoing myocardial revascularization. Esmolol may prove to be of benefit in the treatment of tachycardia and hypertension, thereby preventing myocardial ischemia in the prebypass period. The greater incidence of arrhythmias in the control group seen at aortic dissection may be due to a wearing off of preoperative beta blockade effect at this time. The amount of isoflurane needed to supplement the fentanyl anesthesia was significantly lower in the esmolol group.

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