Anesthesiology
60:455-463, 1984

Influence of Propranolol Plasma Levels on Hemodynamics during Coronary Artery Bypass Surgery

J. Christopher Sill, M.B.B.S., Michael Nugent, M.D.,* Thomas P. Moyer, Ph.D.,† Luis E. Torres, M.D.,‡ Hartzell V. Schaff, M.D.,§ John H. Tinker, M.D.¶*

Hemodynamic effects of propranolol during coronary artery surgery were investigated in 26 patients who chronically took propranolol and who received a standardized morphine/diazepam/pancuronium/halothane anesthetic. Effects were shown by correlating logarithm of the plasma propranolol concentrations *versus* percentage change in hemodynamics following stressful events (induction, intubation, skin incision, sternotomy, and sternal retraction). Log propranolol and hemodynamics following cardiopulmonary bypass also were correlated. A broad range of propranolol levels were observed. Levels (range and mean ± SD) were preinduction 0–96 (25.6 ± 21.6) ng/ml; preincision 0–86 (27.2 ± 24.4) ng/ml; and sternal retraction 0–92 (28.2 ± 25.4) ng/ml. The range of hemodynamic responses to stressful events also was broad. Representative changes between preincision control and sternotomy were (range and mean ± SD): HR −8–30 (7 ± 10) beats/min; PCWP 1–21 (8.5 ± 4.6) mmHg; CI −0.2–1.1 (−0.2 ± 0.7) $l \cdot min^{-1} \cdot m^{-2}$, and SVR −244–1,288 (310 ± 388) $dyn \cdot s \cdot cm^{-5}$. By the time of sternal retraction, CI had declined from preincision values in 14 patients. Linear regression analysis demonstrated an inverse correlation between log propranolol and magnitude of HR, MAP, PCWP, and CI response to stressful stimulation. A direct but statistically weaker correlation with SVR also was seen. Significant correlations between log propranolol *versus* hemodynamic response to anesthetic induction and *versus* postcardiopulmonary bypass hemodynamics were not observed. The authors conclude that propranolol, in proportion to the log plasma level, attenuated stress-induced changes in HR and to a lesser degree changes in MAP, PCWP, and CI and that at higher levels this effect was achieved with some decline in CI and increase in SVR. (Key words: Anesthesia: cardiac. Heart: hemodynamic response to surgery. Intubation, endotracheal: hemodynamic response. Pharmacodynamics: propranolol. Surgery: coronary artery, hemodynamic response. Sympathetic nervous system: beta adrenergic blockade, propranolol.)

CONTINUATION OF PROPRANOLOL THERAPY until the day before or morning of coronary bypass surgery is accepted practice and has been shown to be beneficial for most patients undergoing such surgery.[1-4] In awake humans, propranolol attenuates the heart rate, blood pressure, and cardiac output increases that accompany exertion or emotional stress, thus suppressing a rise in oxygen consumption of the heart and the occurrence of angina.[5-6] The magnitude of these effects has been shown to be related to plasma propranolol level.[7-12] Beneficial effects have been observed from about 10 ng/ml, and a very high degree of beta blockade with marked attenuation of heart rate exercise response has been described at 100 ng/ml.[7-12] Our aim was to determine whether or not plasma propranolol levels and hemodynamic effects were related similarly during anesthesia and surgery. Although previously hemodynamic comparisons have been made between patient groups receiving different perioperative propranolol protocols,[3,4,13-16] to our knowledge hemodynamics and plasma propranolol concentrations have not been correlated. Our purpose was to investigate the correlation between plasma propranolol levels and hemodynamic responsiveness to perioperative stresses. We also wished to determine if at the plasma levels studied, unacceptable cardiovascular depression occurred on anesthetic induction and following cardiopulmonary bypass.

Methods

The investigation was approved by the institutional Human Studies Committee. Informed consent was given by 26 patients, 22 men, and 4 women who were to undergo elective coronary artery bypass graft surgery (CABG) for NYHA Class II–III angina. Patients were excluded from the study if they had left main coronary disease, ejection fraction < 0.4, or unstable angina. All patients had been taking propranolol 40 to 240 mg/day for the previous 1 month to 10 years. Propranolol was continued until the day before or morning of surgery. In addition to propranolol, all patients took dipyridamole (Persantine®; Boehringer Ingelheim Ltd., Ridgefield, Connecticut), and all but one took nitrates, three were receiving a thiazide diuretic, and one procainamide. Apart from these drugs, no other vasoactive medications were being used. No patient had received calcium entry blocking drugs.

We used a standardized anesthetic technique. All patients were premedicated with morphine 10 mg and diazepam 10 mg intramuscularly. Anesthesia was induced with an intravenous infusion of morphine 0.5 mg/kg and diazepam 0.5 mg/kg over 10–15 min while patients

* Assistant Professor of Anesthesiology.

† Assistant Professor of Laboratory Medicine.

‡ Associate Consultant, Department of Anesthesiology. Present address: Los Angeles, California.

§ Assistant Professor of Surgery.

¶ Associate Professor of Anesthesiology. Present address: Professor and Head, Department of Anesthesiology, University of Iowa, Iowa City, Iowa 52242.

Received from the Departments of Anesthesiology, Laboratory Medicine, and Surgery, Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55905. Accepted for publication November 17, 1983. Presented in part at the American Society of Anesthesiologists meeting, Las Vegas, Nevada, September, 1982.

Address reprint requests to Dr. Sill.

breathed 100% oxygen. Endotracheal intubation was performed following paralysis by pancuronium 0.1 mg/kg. Ringer's lactate solution, 400–800 ml, was infused during induction. Following intubation, patients were ventilated with a mixture of oxygen and air (Fi_{O_2} 0.7); no nitrous oxide was used. Halothane was added during surgery and the inspired concentration adjusted to prevent systolic arterial pressure from increasing > 20% above the patients' preoperative levels, measured supine in the patients' hospital rooms the day before surgery.

Hemodynamic data were collected via ECG, radial artery catheters placed prior to anesthetic induction, and via thermodilution pulmonary artery catheters introduced following anesthetic induction and tracheal intubation. Cardiac outputs were determined using iced injectate and an Edwards 9520A® (American Edwards Laboratories, Santa Ana, California) computer with recorder. The initial values were rejected, and the following four determinations were averaged. Hard-copy hemodynamic data were recorded by a calibrated Gould electrostatic system. End-tidal halothane concentrations were measured by a calibrated Beckman LB-2 analyzer. Plasma propranolol concentration was determined from arterial blood, using high-pressure liquid chromatography with fluorescence detection, and pronethalol was an internal standard.[17]

Heart rate and arterial pressure were measured prior to anesthetic induction, following induction, and then 30 s following laryngoscopy and intubation. Heart rate, arterial pressure, right atrial, pulmonary artery, and wedge pressure, cardiac output, and end-tidal halothane concentrations were measured during antiseptic skin preparation approximately 5 min before skin incision. These values were considered to be "control." The measurements were repeated 2 min following sternal skin incision, 1 min following sternotomy, and 3 and 6 min after the beginning of maximum sternal retraction. Following cardiopulmonary bypass, the measurements were performed following aortic decannulation and on skin closure.

Arterial blood samples for later propranolol concentration determination were removed immediately prior to anesthetic induction, prior to skin incision, 6 min after maximum sternal retraction, 10 min following the beginning of cardiopulmonary bypass, at 30° C on rewarming during cardiopulmonary bypass, following aortic decannulation postcardiopulmonary bypass, and finally on skin closure. During the latter part of the study, it became apparent that higher therapeutic range propranolol levels were not present frequently following oral therapy alone. We realized it would be necessary to observe hemodynamic responses throughout a wide range of propranolol blood levels, therefore, 12 of the final 14 patients studied received, in addition to chronic oral propranolol, intravenous propranolol supplementation.[18–20] (It was anticipated that the other 2 of these 14 patients already would have high levels as a consequence of their oral therapy.) Our attempt was not to produce identical plasma levels, but a relatively narrow range of 30–60 ng/ml, and then correlate whatever levels resulted with subsequent hemodynamics. Intravenous dosage was chosen by considering body weight, time elapsed since last oral propranolol dose, and oral dosage given. Thirty minutes before induction, a propranolol bolus of 2–7 mg, at 1 mg/min, was given and then a continuous propranolol infusion of 0.4–0.9 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was begun and continued until the time of cardiopulmonary bypass.[18–20] No propranolol was given during or following bypass.

Data were analyzed by correlating the logarithm of the plasma propranolol concentration *versus* the percentage change in hemodynamics induced by stressful events. Percentage change in HR and MAP from preanesthetic to postanesthetic induction values were correlated with the concurrent log propranolol level as was change in HR and MAP from pretracheal to posttracheal intubation. Hemodynamic parameters were measured immediately prior to skin incision (control) and the percentage change following skin incision, sternotomy, and 3 and 6 min of maximum sternal retraction were correlated with the concurrent log plasma propranolol level. In addition, transient end-tidal halothane concentration and log propranolol were correlated. Cardiac catheterization data and log propranolol levels (preinduction) were examined to determine if preoperative ventricular function and plasma level correlated significantly. Hemodynamics before skin incision (control) and log propranolol were correlated to determine how propranolol affected baseline measurements. Following cardiopulmonary bypass, hemodynamic variables and concurrent log propranolol levels were correlated. Correlations for all the relationships were determined by linear regression and correlation coefficients and P values obtained. Paired t testing was used to compare mean plasma propranolol values measured during the course of anesthesia and surgery. Each value was compared with the previous value and, in addition, postbypass values were compared with that immediately before bypass. When repeated measures were compared, the t test was weighted appropriately with the application of the Bonferroni modification. Throughout statistical analysis, $P < 0.05$ was regarded as significant.

Results

Patients

Demographic data are presented in table 1. Twenty-four patients had three-vessel coronary disease and two had two-vessel disease. Thirteen had suffered previous myocardial infarction and five had a history of hypertension.

TABLE 1. Patient Age and Cardiac Catheterization Data

	Range	Mean ± SD
Age (yr)	40–72	59.9 ± 7.2
Ejection Fraction	0.40–0.69	0.54 ± 0.08
LVEDP (mmHg)	6–30	18.6 ± 7.9

PLASMA PROPRANOLOL LEVELS

Plasma propranolol concentrations are shown in figure 1 (mean ± SE). Little change in mean plasma propranolol concentration occurred between anesthetic induction and cardiopulmonary bypass. Between skin prep and sternal retraction, mean levels differed by only 2.3 ± 4.7 ng/ml (mean ± SD). However, on each occasion, propranolol ranges were marked, concentrations ranging from 0–96 ng/ml at anesthetic induction, 0–86 ng/ml during antiseptic skin prep, and 0–92 ng/ml after 6 min maximum sternal retraction. During cardiopulmonary bypass, levels decreased and were significantly less than prebypass but following bypass the concentrations increased slightly. From the end of bypass to skin closure, the greatest mean level occurred at skin closure, even though no propranolol had been administered in this period.

LOG PROPRANOLOL LEVELS AND HEMODYNAMICS

The effects of propranolol were shown by correlating logarithm of the plasma concentrations *versus* the percentage change in hemodynamic variables occurring following stressful stimulation (induction, intubation, skin incision, sternotomy, 3 and 6 min sternal retraction). Hemodynamics, hemodynamic changes, and correlations with log propranolol levels are shown in tables 2 and 3 and figures 2–9. Although mean hemodynamic values changed little, the range of hemodynamic responses was marked.

Effects of laryngoscopy and tracheal intubation upon HR and MAP are shown in table 2 (mean hemodynamic values) and figure 2 (individual responses). Changes in HR and MAP were suppressed in proportion to the concurrent log propranolol concentration ($P < 0.001$), as can be seen in figures 3 and 4 and in table 2.

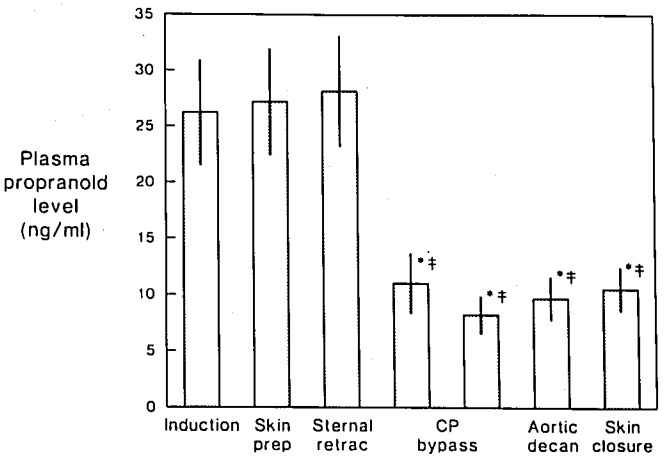

FIG. 1. Plasma propranolol levels (mean ± SE) during the course of anesthesia and surgery. *Indicates significant difference from precardiopulmonary bypass value (at sternal retraction). ($P < 0.001$). †Indicates significant difference from each preceding value ($P < 0.05$). CP = cardiopulmonary bypass.

Hemodynamic effects of skin incision, sternotomy, and sternal retraction are shown in table 3 (mean values) and figure 5 (individual responses from skin preparation control to sternal retraction). Significant inverse correlations between log propranolol concentrations and the magnitude of HR, PCWP, and CI responses were observed. Correlations, r and P values are given in table 3, and relationships following sternal retraction are illustrated in figures 6 to 8. Log propranolol *versus* HR response was consistently the most statistically significant correlation, while those between log propranolol *versus* PCWP and CI changes were of a lesser significance. By the time of sternal retraction, a decline in CI occurred in 14 patients, although cardiac index fell below 2.0 $l \cdot min^{-1} \cdot m^{-2}$ in only one patient, (propranolol level 8 ng/ml). A weak direct correlation ($P < 0.05$) between log propranolol *versus* SVR response was observed following sternotomy and sternal retraction (fig. 9). The relationship between

TABLE 2. Heart Rate and MAP Awake, Postanesthetic Induction and Following Tracheal Intubation. Hemodynamic Changes and Correlations with Concurrent Log Plasma Propranolol Concentrations are Shown

	Hemodynamic Variable	Hemodynamic Δ (range)	Hemodynamic Δ (mean ± SD)	Correlation: Log Propranolol *versus* Per Cent Hemodynamic Δ	*n*	*r*	*P*
Heart rate (beats/min)							
Awake	67 ± 6						
Postanesthetic induction	72 ± 6	−3 to 17	5 ± 5	—	25	−0.05	NS
Laryngoscopy and intubation	81 ± 7	2 to 19	9 ± 5	−10.5X + 25.2	25	−0.63	<0.001
Mean arterial pressure (mmHg)							
Awake	94 ± 14						
Postanesthetic induction	81 ± 13	0 to −30	−13 ± 9	—	25	0.25	NS
Laryngoscopy and intubation	108 ± 22	0 to 60	27 ± 17	−29.9X + 69.3	25	−0.62	<0.001

TABLE 3. Hemodynamic Variables at Control and Following Surgical Stimulation. Hemodynamic Changes (Range and Mean ± SD) Between Control and Points of Surgical Stress are Shown. Correlations Between Concurrent Log Propranolol *versus* Hemodynamic Changes are Shown

	Hemodynamic Variable	Hemodynamic Δ from Control (range)	Hemodynamic Δ from Control (mean ± SD)	Correlation: Log Propranolol *versus* Per Cent Hemodynamic Δ	*n*	*r*	*P*
Heart rate (beats/min)							
Control (skin prep)	69 ± 5						
Skin incision	72 ± 6	−8 to 16	3 ± 5	−8.7X + 15.1	26	−0.66	<0.001
Sternotomy	71 ± 8	−14 to 21	4 ± 8	−14.6X + 20.4	26	−0.70	<0.001
3 min sternal retraction	74 ± 10	−11 to 27	5 ± 10	−19.3X + 31.4	26	−0.75	<0.001
6 min sternal retraction	75 ± 11	−8 to 30	7 ± 10	−21.3X + 36.8	25	−0.80	<0.001
PCWP (mmHg)							
Control (skin prep)	14.3 ± 4.3						
Skin incision	19.2 ± 6.3	−1 to 13	4.9 ± 3.5	−28.5X + 70.5	26	−0.54	<0.01
Sternotomy	19.6 ± 5.3	0 to 12	5.0 ± 3.2	—	25	−0.37	NS
3 min sternal retraction	20.8 ± 6.1	0 to 15	6.6 ± 4.4	−30.2X + 86.5	26	−0.53	<0.01
6 min sternal retraction	22.8 ± 6.9	1 to 21	8.5 ± 4.6	−35.7X + 106.5	26	−0.56	<0.01
CI ($l \cdot min^{-1} \cdot m^{-2}$)							
Control (skin prep)	3.1 ± 0.7						
Skin incision	2.9 ± 0.7	−1.0 to 0.7	−0.2 ± 0.5	—	26	−0.30	NS
Sternotomy	2.8 ± 0.6	−1.6 to 1.3	−0.3 ± 0.7	−22.1X + 19.7	25	−0.57	<0.01
3 min sternal retraction	2.8 ± 0.5	−1.6 to 1.1	−0.2 ± 0.7	−25.8X + 26.1	25	−0.71	<0.001
6 min sternal retraction	2.9 ± 0.6	−0.2 to 1.1	−0.2 ± 0.7	−23.8X + 24.6	25	−0.63	<0.001
SVR ($dyn \cdot s \cdot cm^{-5}$)							
Control (skin prep)	953 ± 181						
Skin incision	1,254 ± 354	−46 to 819	323 ± 238	—	25	−0.10	NS
Sternotomy	1,272 ± 327	−164 to 1,001	320 ± 284	23.9X + 6.4	25	0.45	<0.05
3 min sternal retraction	1,266 ± 371	−188 to 1,698	313 ± 366	30.4X − 1.0	25	0.45	<0.05
6 min sternal retraction	1,262 ± 363	−244 to 1,278	310 ± 338	21.9X + 8.5	25	0.40	<0.05
MAP (mmHg)							
Control (skin prep)	82 ± 11						
Skin incision	98 ± 12	−5 to 37	15 ± 12	—	26	−0.27*	NS*
Sternotomy	95 ± 12	−15 to 29	13 ± 11	—	25	−0.23*	NS*
3 min sternal retraction	98 ± 14	−11 to 40	15 ± 13	—	25	−0.22*	NS*
6 min sternal retraction	96 ± 12	−6 to 46	15 ± 11	—	25	−0.26*	NS*

* During surgery, SBP was prevented from increasing >20% above preoperative levels by administration of halothane, thus a significant correlation between log propranolol *versus* change MAP was not expected.

log propranolol *versus* change in MAP seen on intubation did not continue during surgery because, as a part of the study protocol, systolic BP was prevented from increasing >20% above preoperative value by halothane administration. A weak inverse correlation was observed between log propranolol and end-tidal halothane concentration ($P < 0.05$).

Although we found significant correlations between log propranolol levels and the magnitude of hemodynamic responses to intubation and surgical stimulation, we found no correlation between log propranolol levels and the hemodynamic responses to anesthetic induction. Per cent change in HR and MAP following anesthetic induction did not correlate significantly with log propranolol ($r = -0.05$ and $r = 0.25$, respectively) (table 2).

We found no correlation between log propranolol level measured prior to skin incision and patient's age, myocardial infarction history, LVEDP, or ejection fraction (obtained at cardiac catheterization). In premedicated, resting awake patients prior to anesthetic induction, the correlation log propranolol *versus* HR and MAP was not significant, $r = -0.04$ and $r = -0.08$ respectively. (HR and MAP mean values are shown in table 2, while mean propranolol level appears in fig. 1.) Likewise, in unstimulated, anesthetized patients (end-tidal halothane 0.24 ± 0.10%) in the control period prior to skin incision, no correlation existed between log propranolol and HR, MAP, PCWP, CI, or SVR. Hemodynamic mean values are shown in table 3.

Following cardiopulmonary bypass, no significant relationship was observed between log propranolol levels and hemodynamics (table 4). However in the postbypass period, propranolol levels and ranges were significantly lower than prebypass (fig. 1, table 4). One patient (propranolol level 7 ng/ml) received dopamine to maintain CI above 2.5 $l \cdot min^{-1} \cdot m^{-2}$. Six patients (propranolol range 0–21 ng/ml) received nitroglycerin or nitroprusside to reduce an elevated SVR. Two patients (propranolol

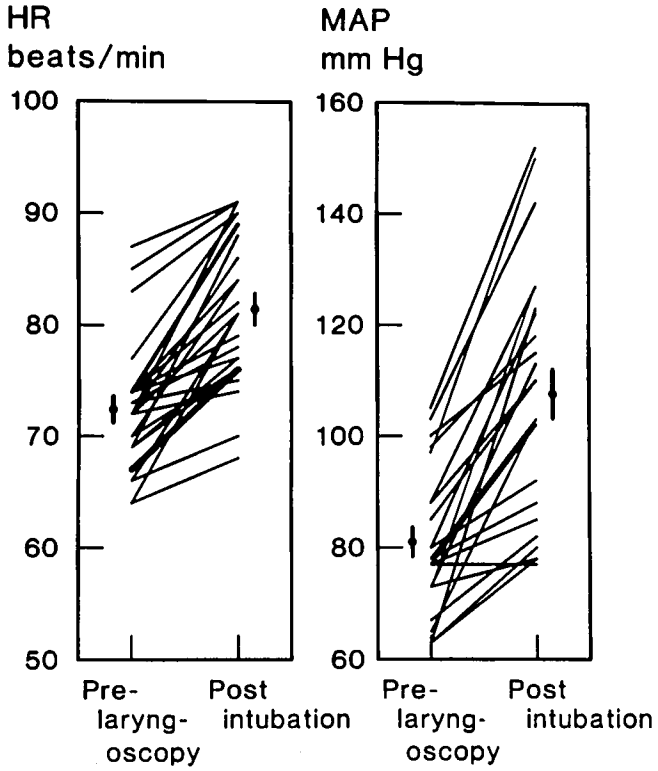

FIG. 2. Individual patient HR and MAP responses between prelaryngoscopy and following tracheal intubation.

levels 0 and 19 ng/ml) were paced electrically to maintain HR above 65 beats/min.

Three patients were excluded from the study. Two developed skin flushing, hypotension, and tachycardia on morphine administration and were treated with phenylephrine. One patient developed PVCs on introduction

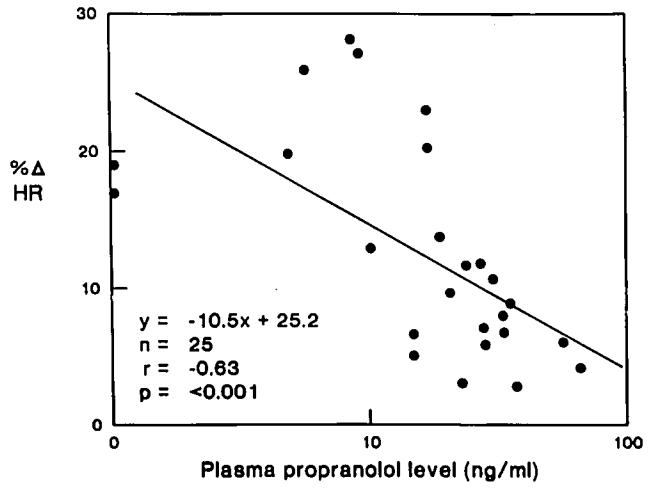

FIG. 3. Correlation per cent HR change from prelaryngoscopy to postintubation *versus* the log plasma propranolol level.

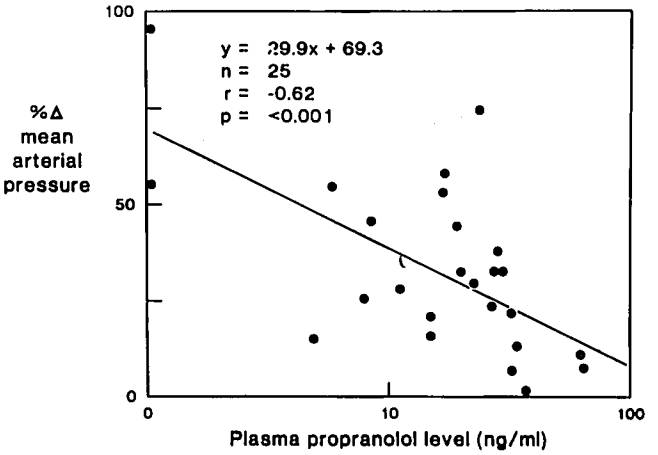

FIG. 4. Correlation per cent MAP change from prelaryngoscopy to postintubation *versus* the log plasma propranolol level.

of halothane. In these instances the anesthetic technique was changed. Occasionally, all hemodynamic or halothane data were not obtained from the remaining 26 patients because of technical mishaps.

Discussion

In patients undergoing CABG surgery, we investigated the correlation between log plasma propranolol level and the magnitude of hemodynamic responses induced by perioperative stresses. Our results demonstrate that responses to tracheal intubation and to surgical stimulation are influenced by propranolol in proportion to the log plasma concentration. Heart rate responses were associated closely with plasma concentration while MAP, PCWP, CI, and SVR changes were associated to a lesser degree.

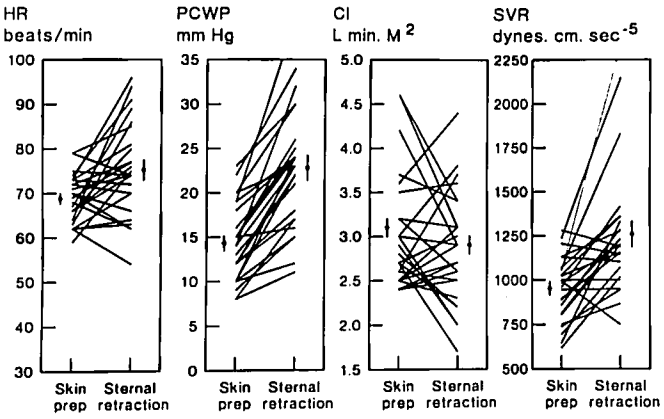

FIG. 5. Individual patient HR, PCWP, CI, and SVR responses between preincision skin preparation control and 6 min following maximum sternal retraction. (MAP response is not included, as halothane was administered to prevent SBP from increasing >20% above preoperative levels.)

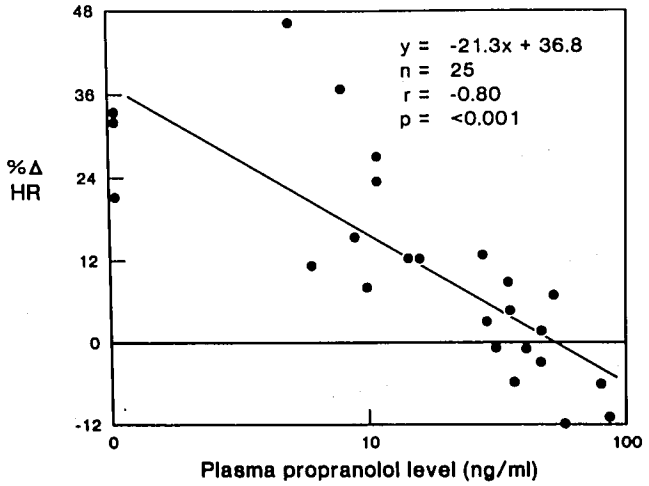

FIG. 6. Correlation between HR response to maximum sternal retraction *versus* concurrent log plasma propranolol level.

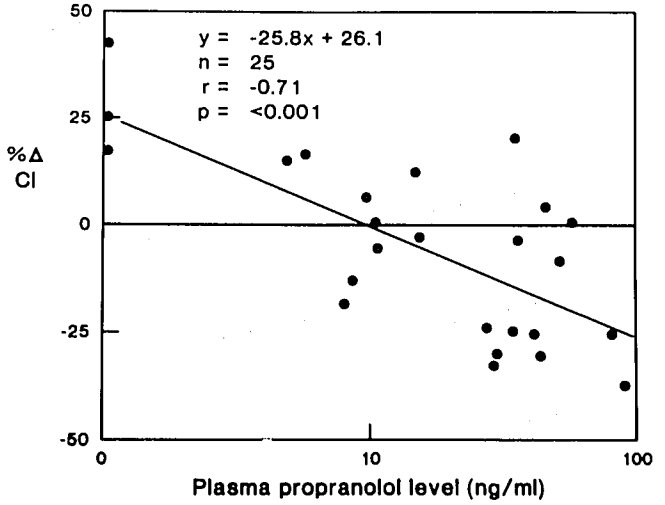

FIG. 8. Correlation between CI response to maximum sternal retraction *versus* concurrent log plasma propranolol level.

Surgery resembles exertional stress as similar increases in sympathetic activity, catecholamine release, and cardiovascular stimulation occur in both situations.[21,22] It is logical, therefore, that propranolol should attenuate the HR response to both exercise stress and to stressful surgical stimulation. We have shown that propranolol suppresses the HR changes induced by laryngoscopy, intubation, and surgical stress in inverse proportion to the drug's log plasma concentration. Mean arterial pressure increases that followed laryngoscopy and intubation were attenuated in a similar way. Such an attenuation is again understandable as, in awake humans, one proposed mechanism of propranolol's antianginal effect is reduction of the blood pressure response to exertion and emotion.

It is less logical that wedge pressure increase should be attenuated by higher propranolol levels, especially as higher levels were associated with greater increases in SVR. However, in patients with coronary artery disease, increase in wedge pressure is a hemodynamic feature of exercise or pacing stress.[23] In the presence of coronary artery disease, sympathetic stimulation and catecholamine release may induce ischemia, worsen regional asynergy, and reduce the rate of ventricular relaxation, even though catecholamines have a positive relaxing effect on isolated cardiac muscle.[24] Propranolol may improve asynergy,[25] improve relaxation rate, and lower wedge pressure.[26] Propranolol also attenuates tachycardia and prolongs diastole, thus permitting greater time for coronary flow.[27] Propranolol may, by relieving ischemia, lower wedge pressure[26]; and presumably prevention of ischemia would prevent wedge pressure increases. During this investi-

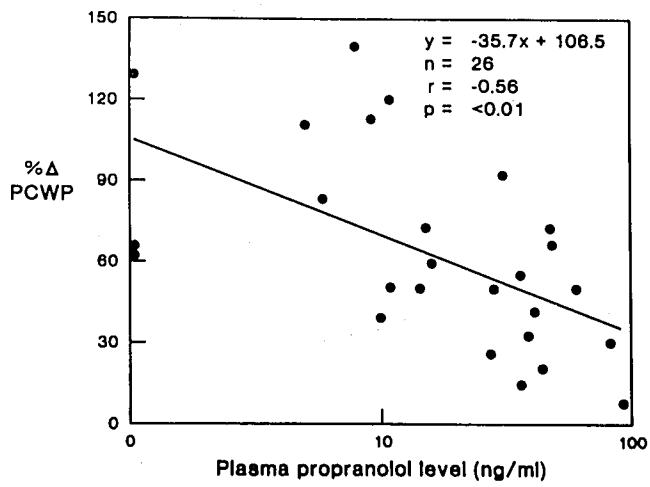

FIG. 7. Correlation between PCWP response to maximum sternal retraction *versus* concurrent log plasma propranolol level.

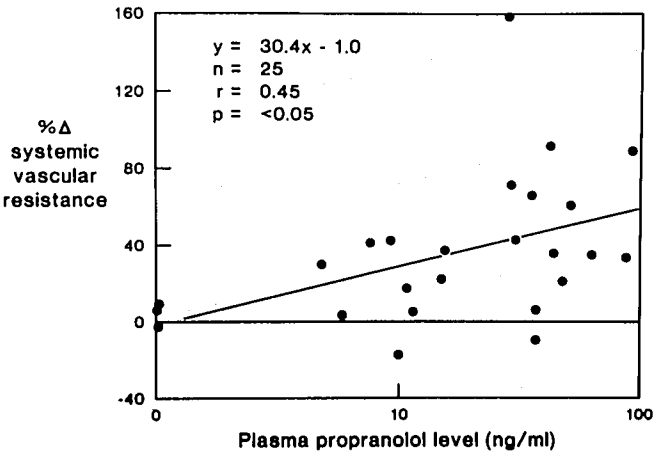

FIG. 9. Correlation between SVR response to maximum sternal retraction *versus* concurrent log plasma propranolol level. Correlation coefficients are lower than those observed for other hemodynamic response *versus* log propranolol level relationships.

TABLE 4. Plasma Propranolol Levels, End-Tidal Halothane Concentrations and Hemodynamic Parameters Following Cardiopulmonary Bypass. No Significant Correlation Between Log Propranolol *versus* Hemodynamics was Observed (Values are Mean ± SD)

	Plasma Propranolol Level (ng/ml)		End-tidal Halothane (%)	HR (beats/min)	MAP (mmHg)	PCWP (mmHg)	CI ($l \cdot min^{-1} \cdot m^{-2}$)	SVR ($dyn \cdot s \cdot cm^{-5}$)
	Range	Mean ± SD						
Aortic Decannulation	0–41	9.7 ± 3.8	0.32 ± 0.14	82 ± 10	88 ± 9	16.5 ± 3.1	3.3 ± 0.7	980 ± 260
Skin Closure	0–38	10.5 ± 3.9	0.36 ± 0.17	83 ± 11	91 ± 8	15.5 ± 2.9	2.8 ± 0.6	1,187 ± 370

gation, greater halothane concentrations were used in patients with lower propranolol levels and this agent's negative inotropic effect may have contributed to wedge pressure increases.

Both resting cardiac index and exercise-induced increase in cardiac index are depressed by propranolol in awake patients. Here, at low propranolol levels, we observed suppression of CI increase following stress, while at greater levels an actual decline in CI occurred. Propranolol blocks both central and peripheral beta-receptors and in the presence of greater propranolol levels, the CI changes may have been mediated by unopposed alpha-adrenergic activity leading to peripheral vasoconstriction. However, halothane-induced vasodilatation may have modified this response. In support of this hypothesis, we observed greater SVR increases in the presence of greater propranolol concentrations. Perhaps a cardioselective beta-blocking drug such as metoprolol would have less effect upon SVR and CI. Heart rate effects also would influence CI.

Although the correlations we have established are statistically significant, for any given propranolol level between-patient variation in response is apparent. This variation is least marked for HR changes but more obvious for changes in SVR where, for example, at a plasma level of approximately 50 ng/ml, the change in SVR ranged from −5 to +160%. Heart rate, MAP, and CI responses correlated more closely with the propranolol level than did PCWP or SVR changes. We believe propranolol is one of several factors that influence hemodynamic performance during anesthesia and surgery and for this reason the correlation coefficients we observed were not always highly significant. In addition, patient age, endogenous catecholamine secretion, beta-receptor number, and sensitivity also contribute to individual variations in propranolol effect.[28]

In awake humans, suppression of exercise-induced tachycardia and reduction in angina frequency have been correlated with the log plasma propranolol level. Plasma levels as low as 8 ng/ml have a measurable effect upon exercise tachycardia; levels of 30 ng/ml reduce angina frequency; and at about 100 ng/ml a high degree of beta blockade exists.[7–12] The correlations we have examined apply to plasma propranolol concentrations from 0 to 96 ng/ml. The effects of higher levels were not investigated. However, it has been suggested that intense beta blockade exists at 80–100 ng/ml and that further increases in plasma level produce little further log concentration-related effect, *i.e.*, a plateau for propranolol effect occurs at about 100 ng/ml.[7–12,28]

Our observations that HR and MAP in the resting awake patient correlate poorly with log propranolol levels has been reported previously.[9,11,29] This finding implies that it may be difficult to judge a patient's degree of beta blockade simply by observing heart rate. Lack of correlation may be explained by the predominance of parasympathetic tone and low sympathetic activity while at rest.[30]

Surprisingly, we found no significant correlation between log plasma propranolol level and changes in HR or decrease in MAP during induction of anesthesia. Greater HR and MAP decreases did not occur in the presence of greater propranolol levels. Pancuronium effect on HR did not correlate with propranolol level. We found no relationship between hemodynamic state and log propranolol level in the surgically unstimulated patient during light halothane anesthesia. A similar lack of significant correlation existed during light halothane anesthesia following cardiopulmonary bypass, but at this time the propranolol concentrations investigated were low. (However, Wechsler[16] has described increased postbypass inotropic requirements in patients maintained upon 320 to 480 mg propranolol/day until the time of surgery.) Lack of correlation between hemodynamic change on anesthetic induction and with hemodynamics following bypass implies that continuing propranolol until the time of surgery, as most clinicians do, may not be hazardous as the warning on the package insert insists.

During data analysis, patients given supplemental intravenous propranolol were not separated from those who had received oral propranolol only. It has been contended that a difference in beta blockade efficacy exists when propranolol is given orally *versus* intravenously.[31] This difference occurs predominantly when oral propranolol has been administered acutely because, in this situation, hepatic metabolism generates 4-hydroxy propranolol and other vasoactive metabolites. Subsequently, it has been agreed by most investigators that, during long-

term oral therapy, vasoactive metabolite levels decline and any contribution to overall propranolol effect probably is negligible.[12,29,32] Our patients had all received long-term oral therapy, and following such therapy it is believed that propranolol's effectiveness is a predictable function of its plasma concentration according to the classical drug-receptor theory for competitive antagonism.[7,29,33]

Our results are in agreement with those of Prys-Roberts,[13] who found that beta blockade attenuates HR and MAP response to intubation. We are not in agreement with McCammon *et al.*[14] who did not demonstrate such an action. Perhaps measurement of actual plasma propranolol levels in the latter study would have helped resolve this apparent conflict. Measurement of propranolol levels may be useful when anesthetic techniques are investigated and compared, as differing degrees of background beta blockade would influence hemodynamic results. A knowledge of patient propranolol levels during investigations of high-dose fentanyl anesthesia may have helped resolve the controversy concerning the ability of fentanyl to suppress hemodynamic responses to surgical stimuli.[34] Again, differences in background beta blockade may have contributed variations in different investigators' experiences. Safwat *et al.*[15] reported that very small intravenous propranolol doses (0.5 mg)—an amount unlikely to produce persistent therapeutic plasma levels—suppress HR and BP response to surgery. At first glance, these results are not in agreement with the present study, however, propranolol's effectiveness closely follows the time course of the plasma level. Following even a small bolus injection, the concentration would be initially high and produce an appropriately marked effect.[29,33]

As might be expected, propranolol levels decreased during cardiopulmonary bypass, however, following bypass we noticed an interesting aspect of propranolol kinetics—levels increased slightly. This observation has been reported previously, and it may be due to redistribution of propranolol from the tissues (probably the lungs).[35]

We conclude that concurrent plasma propranolol concentration is a major factor influencing hemodynamic responsiveness to stressful stimulation during anesthesia for CABG surgery. Propranolol, in proportion to its log plasma level, attenuated stress-induced increases in HR, MAP, PCWP, and CI. Individual variation in propranolol effect occurred, this being most apparent for PCWP and SVR changes. Despite greater halothane use in patients with lower propranolol levels, hemodynamic changes in this situation were more marked. We believe beneficial propranolol effects observed in awake humans continue during surgery, but that at greater plasma levels they were achieved at the expense of some increase in SVR and decrease in CI. We also believe that propranolol, in the plasma range investigated, is not associated necessarily with unacceptable cardiovascular depression on anesthetic induction, during anesthesia, or following cardiopulmonary bypass.

The authors wish to thank Ms. Harriet Morrow, Ms. Julie Vogen, and Mr. Edward Thompson for their assistance.

References

1. Jones EL, Kaplan JA, Dorney ER, King SB: Propranolol therapy in patients undergoing myocardial revascularization. Am J Cardiol 38:696–700, 1976
2. Slogoff S, Keats AS, Ott E: Preoperative propranolol therapy and aortocoronary bypass operation. JAMA 240:1487–1490, 1978
3. Kopriva CJ, Brown AC, Pappas G: Hemodynamics during general anesthesia in patients receiving propranolol. ANESTHESIOLOGY 48:28–33, 1978
4. Oka Y, Frishman W, Becker RM: Clinical pharmacology of the new beta adrenergic blocking drugs. Part 10. Beta-adrenoreceptor blockade and coronary artery surgery. Am Heart J 99:255–269, 1980
5. Prichard BNC, Gillam PMS: Assessment of propranolol in angina pectoris: clinical dose-response curve and effect on electrocardiogram at rest and on exercise. Br Heart J 33:473–480, 1971
6. Dwyer EM, Wiener L, Cox JW: Effects of beta adrenergic blockade (propranolol) on left ventricular hemodynamics and the electrocardiogram during exercise-induced angina pectoris. Circulation 38:250–268, 1968
7. Nies AS, Shand DG: Special article: Clinical pharmacology of propranolol. Circulation 52:6–15, 1975
8. Chidsey C, Pine M, Favrot L, Smith S, Leonetti G, Morselli P, Zanchetti A: The use of drug concentration measurements in the studies of the therapeutic response to propranolol. Postgrad Med J 52:26–32, 1976
9. Pine M, Favrot L, Smith S, McDonald K, Chidsey CA: Correlation of plasma propranolol concentration with therapeutic response in patients with angina pectoris. Circulation 52:886–893, 1975
10. Mullane JF, Kaufman J, Dvornik D, Coelho J: Propranolol dosage, plasma concentration, and beta blockade. Clin Pharmacol Ther 32:692–700, 1982
11. Adlerman EL, Davis RO, Crowley JJ, Lopes MG: Dose response effectiveness of propranolol for the treatment of angina pectoris. Circulation 51:964, 1975
12. Shand DG: Pharmacokinetic properties of the beta adrenergic receptor blocking drugs. Drugs 7:39–47, 1974
13. Prys-Roberts C, Foex P, Biro GP, Roberts JG: Studies of anaesthesia in relation to hypertension. V. Adrenergic beta-receptor blockade. Br J Anaesth 45:671–681, 1973
14. McCammon RL, Hilgenberg J, Stoelting RK: Effect of propranolol on circulatory responses to induction of diazepam-nitrous oxide anesthesia and endotracheal intubation. Anesth Analg 60:579–583, 1981
15. Safwat AM, Reitan JA, Misle GR, Hurley EJ: Use of propranolol to control rate-pressure product during cardiac anesthesia. Anesth Analg 60:732–735, 1981
16. Wechsler AS: Assessment of prospectively randomized patients receiving propranolol therapy before coronary bypass operation. Ann Thorac Surg 30:128–136, 1980
17. Jetlow P, Bush W, Hochster H: Improved liquid chromatographic determination of propranolol in plasma, with fluorescence detection. Clin Chem 25:777–779, 1979

18. Wells PH, Hug CC, Kaplan JA: Maintenance of propranolol therapy by IV infusion. ANESTHESIOLOGY 53:S128, 1980
19. Chidsey CA, Morselli P, Bianchetti G, Morganti A: Studies of the absorption and removal of propranolol in hypertensive patients during therapy. Circulation 52:313–318, 1975
20. McAllister RG: Intravenous propranolol administration: A method for rapidly achieving and sustaining desired plasma levels. Clin Pharmacol Ther 20:517–523, 1976
21. Halter JB, Pflug AE, Porte D: Mechanism of plasma catecholamine increases during surgical stress in man. J Clin Endocrinol 45:936–944, 1977
22. Galbo H, Holst J, Christensen NJ: Glucagon and plasma catecholamine responses to graded and prolonged exercise in man. J Appl Physiol 38:70, 1975
23. Grossman W, Barry HB: Diastolic pressure-volume relations in the diseased heart. Fed Proc 39:148–155, 1980
24. Brutsaert DL, Housmans PR, Goethals MA: Dual control of relaxation. Circ Res 47:637–652, 1980
25. Vatner SF, Baig H, Manders WT, Ochs H, Pagani M: Effects of propranolol on regional myocardial function, electrograms, and blood flow in conscious dogs with myocardial ischemia. J Clin Invest 60:353–360, 1977
26. Mueller HS, Ayres SM: The role of propranolol in the treatment of acute myocardial infarction. Prog Cardiovasc Dis 19:405–412, 1977
27. Boudoulas H, Lewis RP, Rittgers SE, Leier CV, Vasko JS: Increased diastolic time: A possible important factor in the beneficial effect of propranolol in patients with coronary artery disease. J Cardiovasc Pharmacol 1:503–513, 1979
28. Johnsson G, Regårdh CG: Clinical pharmacokinetics of beta-adrenoreceptor blocking drugs. Clin Pharmacokinet 1:233–263, 1976
29. McDevitt DG: The assessment of beta adrenoceptor blocking drugs in man. Br J Clin Pharmacol 4:413–425, 1977
30. Robinson BF, Epstein SE, Beiser GD, Braunwald E: Control of heart rate by the autonomic nervous system: Studies in man on the interration between baroreceptor mechanisms and exercise. Circ Res 19:400–411, 1966
31. Coltart DJ, Shand DG: Plasma propranolol levels in the quantitative assessment of beta adrenergic blockade in man. Br Med J 3:731–734, 1970
32. Cleaveland CR, Shand DG: Effect of route of administration on the relationship between beta adrenergic blockade and plasma propranolol level. Clin Pharmacol Ther 13:181–185, 1972
33. McDevitt DG, Shand DG: Plasma concentrations and the time course of beta-blockade due to propranolol. Clin Pharmacol Ther 18:708–713, 1975
34. Lowenstein E, Philbin DM: Narcotic "anesthesia" in the eighties. ANESTHESIOLOGY 55:195–197, 1981
35. Plachetka JR, Salomon NW, Copeland JG: Plasma propranolol before, during, and after cardiopulmonary bypass. Clin Pharmacol Ther 6:745–751, 1981