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Interaction of Anesthesia, Beta-receptor Blockade, and Blood Loss in Dogs with Induced Myocardial Infarction

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The cardiovascular effects of halothane–nitrous oxide anesthesia, and beta-receptor blockade with either propranolol or practolol, were studied in 15 dogs in which severe myocardial infarction had been induced ten days earlier. The hemodynamic responses to blood loss amounting to 25 per cent of estimated blood volume, and its subsequent replacement, were studied before and after induction of beta-receptor blockade. In terms of cardiac output and aortic blood flow acceleration, cardiac performance in the absence of beta-blockade was markedly impaired during steady-state anesthesia, compared with corresponding values in normal dogs. Practolol (2.0 mg/kg) administered during anesthesia induced no significant circulatory change other than a 14 per cent decrease in heart rate and a 25 per cent increase in stroke volume. Propranolol (0.3 mg/kg) caused a comparable reduction of heart rate, but significantly reduced cardiac output (−27 per cent), aortic blood flow acceleration (−26 per cent), and peak LV power (−19 per cent), and increased systemic vascular resistance (+49 per cent). The two drugs caused comparable shifts of the isoproterenol dose–response curve during anesthesia. Graduated blood loss during anesthesia, to a total of 25 per cent of blood volume, caused consistent circulatory changes (decreased mean arterial pressure, cardiac output, peak LV power, LV minute work) that were essentially similar before and after beta-receptor blockade with either propranolol or practolol. The positive inotropic effect of calcium gluconate during halothane anesthesia was significantly reduced following either propranolol or practolol, but the hemodynamic responses to changes of systemic vascular resistance induced with acetylcholine or phenylephrine were not modified by beta-receptor blockade. (Key words: Heart, myocardial infarction; Hemorrhage, propranolol; Sympathetic nervous system, beta-adrenergic blockade; Anesthetics, volatile, halothane.)

ADRENERGIC beta-receptor-blocking drugs are widely used in the management of patients who have hypertension and the various manifestations of ischemic heart disease. Increasing numbers of patients receiving these drugs need anesthesia for surgical procedures both related to and incidental to their coronary-artery disease. While there is evidence that hypertensive patients benefit from maintenance of beta-receptor blockade during anesthesia and operation,[1] many investigators have advocated withdrawal of beta-receptor blocking drugs 24 hours to a week prior to elective operations.[2–6] Others have stated that so long as beta-receptor blocking drugs are recognized as potent suppressors of adrenergic activity, and their pharmacology, together with that of the anesthetic drugs, is taken into account, anesthesia of patients receiving long-term beta-receptor-blocking therapy should not present a major hazard.[7–9] The adverse consequences of sudden withdrawal of beta-receptor-blocking drugs from patients who have ischemic heart disease have been emphasized.[10–12] Thus, powerful arguments must be presented for the routine withdrawal of beta-receptor-blocking drugs prior to operation. One commonly stated, but unsubstantiated, argument has been that patients receiving beta-receptor-blocking drugs have im-

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paired ability to compensate for blood loss or hypoxemia during anesthesia.[7,13–15]

To circumvent the problems inherent in studying deliberate blood loss in man during surgical procedures, we used an animal model to recreate the "worst possible" situation in human anesthesia, that of the patient who has a history of myocardial infarction or ischemic heart disease, is receiving beta-receptor blocking drugs, needs surgical treatment and anesthesia, and may lose a significant part of his blood volume due to surgical hemorrhage. We sought also to compare the hemodynamic responses to anesthesia and hemorrhage in the presence of two different beta-receptor blockers, propranolol and practolol, the latter being relatively cardioselective and having some intrinsic sympathomimetic activity.

Methods

Twenty healthy mongrel dogs weighing between 9.6 and 16.0 kg were anesthetized with thiopental (15 mg/kg). The tracheas were intubated and the dogs artificially ventilated with 1.0 per cent halothane in nitrous oxide (66 per cent) and oxygen. Under sterile conditions, a left lateral thoracotomy was performed, with excision of the fifth rib. An electromagnetic flow transducer (SE Laboratories, model 230) was implanted around the ascending aorta; in the last 14 dogs a thin sleeve of woven dacron was interposed between the transducer and the aortic wall. A miniature pressure transducer (Konigsberg Instruments, Model P 19) was implanted into the left ventricular cavity through an apical incision. PVC catheters (Portex Plastics, umbilical catheter 6FG) were implanted into the left atrium through the atrial appendage, into the pulmonary artery by way of the right ventricular infundibulum, and into the ascending aorta through the omohyoid artery (approached by a separate cervical incision).

Following these implantations, a series of measurements from the appropriate transducers was made. Ligatures were then placed around three left ventricular branches of the left anterior descending coronary artery, and during continuous monitoring of cardiac function each ligature was tied in turn, a 5-minute period being allowed between successive coronary-artery occlusions. When it was clear that the animal had tolerated the immediate effects of occlusion, and that a significant reduction of cardiac function had been achieved, the chest incision was closed and the catheters and leads buried under the skin of the neck. The dogs were allowed to recover for seven to ten days, and daily assessments of their general condition were made, supported by blood sampling for biochemical, hematologic and blood-gas estimations.

Three dogs died during the surgical procedure as a result of ventricular fibrillation secondary to the coronary-artery ligations. Two dogs died during the first postoperative week as a result of rupture of the ascending aorta due to erosion by the flow transducer; no death from this cause occurred following use of the interposed dacron sleeve.

The 15 surviving dogs were divided into a group of seven which received practolol intravenously, and a group of eight which received propranolol intravenously. In four of the dogs subsequently given practolol, whose leads and catheters had been exteriorized from the outset, measurements were made in the conscious, resting animal before, during, and after induction and maintenance of anesthesia. Subsequently these four animals were treated in the same way as the others. Anesthesia was induced with thiopental (10 mg/kg, iv) and, after endotracheal intubation, was maintained with 1 per cent halothane in nitrous oxide (66 per cent) and oxygen (33 per cent). Artificial ventilation was maintained with a constant-volume ventilator (Oxford Ventilator, Penlon Ltd., U.K.) set to provide a tidal volume of 40 ml/kg at a rate of 12/min. Arterial blood P_{CO_2} was maintained at 40 ± 2 mm Hg by adding a low concentration of carbon dioxide to the inspired gas mixture, and using an infrared CO_2 analyzer to give a continuous indication of end-expiratory P_{CO_2}. Steady-state anesthesia was established for 90 minutes before the first set of control hemodynamic measurements was made. Subsequently the following protocol was instituted.

1) Responses of hemodynamic variables to intra-aortic injection of a single dose of acetylcholine (5 μg/kg) were recorded, peak responses occurring 30–45 seconds after injection.

2) Hemodynamic responses to intra-aortic

injection of a single dose of phenylephrine hydrochloride (4 μg/kg) were recorded, peak responses occurring within 90 seconds; return to baseline levels of the recorded variables was achieved within 5 to 10 minutes.

3) Hemodynamic responses to intravenous injection of calcium gluconate (30 mg/kg) were recorded, peak responses occurring within 30 seconds of injection.

4) Chronotropic and inotropic responses to a series of separate 2-minute infusions of isoproterenol hydrochloride in saline solution (0.25, 0.5, 1.0, 2.0, 4.0, and 8.0 μg/kg/min) were studied, allowing dose–response curves to be constructed before and after the subsequent beta-receptor blockade.

5) After these drug interventions, the dogs were allowed to settle for 15 minutes before a set of pre-hemorrhage control hemodynamic values was obtained. Blood was then removed from the aortic catheter and stored in a sterile heparinized bottle suspended in a water bath maintained at 38 C. The volume withdrawn was based on an assumed blood volume of 85 ml/kg[16,17]. Ten per cent of the estimated blood volume was withdrawn, followed by an equilibration period of 10 minutes, at the end of which a set of measurements was made. A further 10 per cent of blood volume was then withdrawn and further measurements made after 10 minutes. Finally, a further 5 per cent of blood volume was withdrawn, making a total of 25 per cent of the animal's estimated blood volume, and 30 minutes after the initial withdrawal a final set of measurements was made. The blood that had been withdrawn was then rapidly restored by infusion and measurements of hemodynamic variables were made 10 and 20 minutes later. Samples of arterial and mixed venous blood were withdrawn in the control period, after withdrawal of 25 per cent of blood volume, and 20 minutes after restoration of blood.

Following these interventions, three dogs in the practolol group were allowed to recover consciousness. They were subsequently treated with practolol (5 mg/kg, orally, twice a day) for at least four days. The second part of the protocol, described below, was then followed in these animals, together with the other four animals, in which a period of 15 minutes was allowed before a complete set of measurements, including blood-gas estimations, was obtained. Seven animals were thus given practolol (2.0 mg/kg) intravenously, and eight animals were given propranolol (0.3 mg/kg) intravenously. These doses were selected on the basis of previous studies that indicated that a shift of the midpoint of the isoproterenol dose–response curve of 1 to 1.5 orders of magnitude could be achieved.

The complete protocol of steady-state anesthesia, the interventions of acetylcholine, phenylephrine, and calcium gluconate, isoproterenol dose–response curves, and the hemorrhage sequence, was then repeated. Thus, with each animal acting as its own control, the cardiovascular interactions of anesthesia, hemorrhage and beta-receptor blockade were studied in seven dogs given practolol and eight dogs given propranolol.

At the end of each study, the dog was sacrificed and a careful examination of the thoracic contents was made, with special reference to the state of the left ventricle and the extent of the induced infarct. In every animal, an extensive anterolateral infarct of the whole thickness of the left ventricular wall was found, with consistent involvement of the ventricular septum and its adjoining papillary muscle. Rupture of the papillary muscle was not observed in any animal. No other relevant pathologic change was observed, and all catheters were patent and free of thrombus.

Measurements

The left ventricular pressure signal derived from the implanted transducer was calibrated *in vivo* on the basis of two assumptions: that peak left ventricular pressure was the same as peak aortic pressure, and that left ventricular end-diastolic pressure was equal to mean left atrial pressure. Confirmation that this method of calibration was accurate was obtained in other dogs by advancing a catheter from the carotid artery into the left ventricle, and using a Statham P23De transducer to calibrate the Konigsberg transducer. The first derivative of left ventricular pressure (dP/dt) was obtained with an analog-differentiating circuit[18] and the index Max LV(dP/dt)/DP (where DP is the developed pressure at the time of maximum dP/dt) was derived as a measure of changes in myocardial contractility.[19–20] Aortic, pul-

monary arterial, and left atrial pressures were measured with Statham P23De transducers. Aortic blood flow velocity was measured with a sine-wave electromagnetic flowmeter (SE Laboratories, Model 275), and stroke volume was derived by an integrating circuit. Acceleration of blood flow in the aorta was derived from the aortic blood flow velocity signal using a differentiating circuit similar to the one used for ventricular dP/dt. Aortic blood flow was calibrated by comparing the mean time integral of the aortic blood flow velocity signal with the average stroke volume simultaneously derived from three indicator-dilution curves inscribed following pulmonary arterial injection and aortic sampling and detection of indocyanine green. The electrocardiogram was derived from standard limb leads. All variables were inscribed on an eight-channel ink-jet recorder (Elema-Schonander, Model EM81). From the recorded traces, values of peak aortic pressure, peak aortic blood flow, mean arterial pressure, stroke volume, and heart rate were used to compute cardiac output, systemic vascular resistance, peak left ventricular power (watts) and left ventricular stroke work and minute work (joules).

Samples of arterial and mixed venous blood were analyzed for pH, P_{CO_2} and P_{O_2} using conventional electrode systems and amplifiers.[21-22] Hemoglobin concentrations were measured by the cyanmethemoglobin method, and these values were used to calculate oxygen contents of arterial and mixed venous blood[23] using the oxyhemoglobin-dissociation curve for the dog.[24] From the values of cardiac output and arteriovenous oxygen content, oxygen uptake ($\dot{V}_{O_2}$) was calculated and expressed in ml/min/kg STPD.

Results

Hemodynamic Effects of Coronary-artery Occlusion during Anesthesia

Table 1 summarizes percentage changes of hemodynamic variables recorded before and 20 minutes after ligation of the third branch of the left anterior descending coronary artery. Cardiac function was markedly impaired, as shown by the 20–30 per cent reductions of Max LV dP/dt, aortic blood flow acceleration, and cardiac output, associated with elevated left ventricular end-diastolic pressure (LVEDP). The electrocardiographic changes associated with this series of ligations are shown in figure 1.

TABLE 1. Changes of Hemodynamic Values as a Result of Coronary-arterial Ligation in 13 Dogs*

	Mean Change from Control (Per Cent)	Significance
Peak LV pressure	−15	$P < 0.05$
Max LV dP/dt	−22	$P < 0.05$
Peak aortic blood flow	−25	$P < 0.001$
Aortic blood flow acceleration	−23	$P < 0.005$
Stroke volume	−30	$P < 0.005$
Heart rate	+17	$P < 0.001$
Cardiac output	−20	$P < 0.01$

* Percentage changes are shown because some of the variables were not directly calibrated in absolute values at the time of ligation.

Late Hemodynamic Effects of Myocardial Infarction

Values of hemodynamic variables measured during steady-state anesthesia in the 15 dogs with myocardial infarction were compared with values obtained in a different series of dogs with normal hearts under similar conditions of anesthesia.[25] Although the values of Max LV(dp/dt)DP were similar in the two groups, cardiac output was less, but not significantly so, in the dogs with myocardial infarction (137 ml/min/kg, SD 48) than in the normal dogs (160 ml/min/kg, SD 48), whereas aortic blood flow acceleration was significantly less in the infarcted dogs (3,368 ml.sec^{-2}, SD 1,105) than in the normal dogs (5,345 ml.sec^{-2}, SD 1,588).

Comparison of Data from Conscious and Anesthetized Dogs

Table 2 summarizes hemodynamic variables in four conscious, tranquil dogs with myocardial infarction and with exteriorized leads and catheters before induction of anesthesia, and the corresponding values after steady-state anesthesia had been established for 90 minutes. Mean arterial pressures and heart rates were similar under the two con-

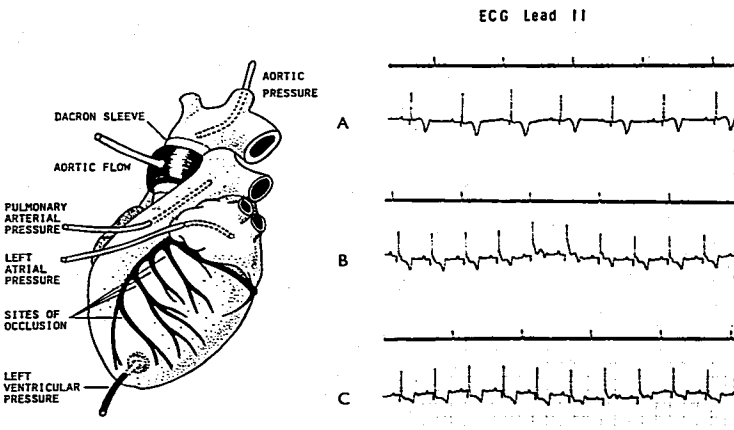


FIG. 1. Diagram of instrumentation implanted in the dogs' hearts and of the sites of ligation of coronary arteries. The right panel shows the typical ECG changes (Lead II) resulting from such ligations. *A*, before ligation; *B* and *C*, 10 and 20 minutes after ligation, respectively.

ditions, but cardiac output decreased by 35 per cent, almost entirely due to a reduction of stroke volume. These changes were associated with significant reduction of aortic blood flow acceleration and elevation of LVEDP.

EFFECTS OF BETA-RECEPTOR BLOCKADE DURING HALOTHANE–NITROUS OXIDE ANESTHESIA

Practolol (2.0 mg/kg, iv) (Table 3). In seven dogs, heart rate decreased 14 per cent, whereas stroke volume increased 25 per cent, resulting in a small but not statistically significant increase of cardiac output, and little change of either mean aortic pressure or left ventricular end-diastolic pressure. These changes were associated with small but insignificant increases in indices of myocardial contractility: peak aortic flow (+7 per cent), Max LV power (+9 per cent), Max aortic blood flow acceleration (+6 per cent) and Max LV(dP/dt)/DP (+4 per cent).

Propranolol (0.3 mg/kg, iv) (Table 3). In eight dogs, heart rate decreased 17 per cent and stroke volume was reduced 13 per cent, resulting in a significant reduction of cardiac output (−27 per cent) but no significant reduction of mean arterial pressure. These changes indicated a 49 per cent increase of systemic vascular resistance. In contrast to the changes observed during practolol administration, the indices of changes in myocardial contractility indicated a significant ($P < 0.05$) reduction: peak aortic flow (−19 per cent), Max LV power (−19 per cent), Max aortic blood flow acceleration (−26 per cent) and Max LV(dP/dt)/DP (−11 per cent).

RESPONSES TO ISOPROTERENOL

The isoproterenol dose–response curves constructed from the chronotropic and inotropic responses to isoproterenol infusion during anesthesia before and after beta-receptor blockade with practolol and with propranolol indicated that significant and comparable extents (>1 order of magnitude) of competitive antagonism at beta-receptive sites were achieved with the chosen doses of practolol and propranolol (fig. 2).

RESPONSES TO ACETYLCHOLINE

Intra-arterial injection of acetylcholine during anesthesia caused reductions (50 per cent)

of systemic vascular resistance ($P < 0.005$) in all animals, before and after practolol or propranolol, associated with reductions of both mean and diastolic arterial pressures ($P < 0.001$). Heart rate did not change in response to acetylcholine in either group of dogs prior to beta-receptor blockade, but there were small (5 per cent) but significant ($P < 0.05$) increases of heart rate in both groups after beta-receptor blockade. There was no significant change in either index of myocardial contractility, Max LV (dP/dt)/DP or aortic blood acceleration, yet acetylcholine caused increases in both stroke volume and cardiac output ($P < 0.001$) before and after both propranolol and practolol.

Responses to Phenylephrine

In contrast to the effect of acetylcholine, intra-arterial injection of phenylephrine during anesthesia caused increases of systemic vascular resistance (49–67 per cent; $P < 0.01$) before and after both practolol and propranolol, associated with elevations of mean arterial pressure (27–31 per cent; $P < 0.01$). In both groups of dogs prior to beta-receptor blockade there were reductions ($P < 0.01$) of heart rate (12–13 per cent), indicating active baroreceptor reflex slowing of heart rate. No significant change of heart rate occurred in either of the beta-receptor-blocked groups of dogs. No significant change of LV(dP/dt)/DP occurred in any group. However, the reductions ($P < 0.01$) of aortic blood flow acceleration (19–25 per cent) despite an increase of LVEDP (from 5–8 to 12–15 mm Hg) in both blocked and unblocked dogs probably reflect the increases in afterload (SVR). Stroke volume and cardiac output were reduced (−16 to −22 per cent, $P < 0.05$) before and after both beta-receptor blockers. There was no difference in the responses to phenylephrine infusion during anesthesia as a result of beta-receptor blockade with either practolol or propranolol other than the heart rate changes already referred to.

Responses to Calcium Gluconate

The main effects of calcium gluconate administered during anesthesia were: 1) significant increases of myocardial contractility, as reflected by the changes of Max LV(dP/dt)/DP (+19 to +35 per cent), and aortic blood flow acceleration (+54 to +74 per cent). The increase in Max LV(dP/dt)DP resulting from calcium gluconate injection was significantly greater ($P < 0.05$) in the unblocked animals (23–35 per cent) compared with the increase after practolol (+19 per cent) or propranolol (+19 per cent). Correspondingly, the increases in aortic blood flow acceleration induced by calcium gluconate were significantly less ($P < 0.05$) after practolol (+60 per cent, compared with 74 per cent in the unblocked animals), and after propranolol (+54 per cent, compared with +61 per cent in the unblocked animals).

2) As a result of the increased myocardial contractility, both stroke volume and cardiac output showed significant increases (19–30 per cent) in response to calcium gluconate, although no significant difference between unblocked and beta-blocked animals was detected.

Hemodynamic Responses to Graded Hemorrhage

The main hemodynamic responses to 25 per cent reduction of blood volume during anes-

TABLE 2. Hemodynamic Variables, Awake and after 90 Minutes of Maintenance Anesthesia in Four Dogs (Means ± SD)

	Awake	Anesthetized	Significance
Heart rate (beats/min)	131 (4)	135 (22)	NS
Mean arterial pressure (mm Hg)	86 (13)	85 (26)	NS
Stroke volume (ml)	20.2 (5.4)	12.1 (5.1)	$P < 0.025$
Cardiac output ($ml \cdot min^{-1} \cdot kg^{-1}$)	192 (59)	125 (55)	$P < 0.025$
SVR ($dyn \cdot sec \cdot cm^{-5}$)	2,804 (1,087)	4,752 (2,050)	NS
Max LV(dP/dt)/DP (sec^{-1})	43.5 (11.0)	37.7 (4.5)	NS
Aortic blood flow acceleration ($ml \cdot sec^{-2}$)	8,036 (1,806)	3,475 (1,087)	$P < 0.025$
LVEDP (mm Hg)	1.0 (1.0)	6.0 (3.0)	$P < 0.05$

TABLE 3. Hemodynamic Effects of Beta-receptor Blockade Induced with Practolol or Propranolol during Anesthesia with Halothane–Nitrous Oxide (Means ± SD)

	Practolol-treated Dogs (n = 7)			Propranolol-treated Dogs (n = 8)		
	Before	After	Significance of Difference	Before	After	Significance of Difference
Heart rate (beats/min)	135 (21)	116 (19)	$P < 0.025$	141 (24)	117 (24)	$P < 0.01$
Stroke volume (ml/kg)	0.9 (0.4)	1.2 (0.4)	$P < 0.05$	1.2 (0.3)	1.0 (0.4)	N.S.
Cardiac output (ml/min/kg)	125 (55)	132 (37)	N.S.	169 (63)	124 (62)	$P < 0.05$
Aortic pressure						
Systolic (mm Hg)	107 (26)	109 (22)	N.S.	110 (14)	109 (24)	N.S.
Diastolic (mm Hg)	73 (27)	71 (24)	N.S.	75 (14)	69 (17)	N.S.
Systemic vascular resistance (dyn·sec·cm^{-5})	4,752 (775)	4,288 (659)	N.S.	3,948 (975)	5,869 (1,145)	$P < 0.05$
LVEDP (mm Hg)	6 (3)	7 (3)	N.S.	7 (5)	10 (4)	N.S.
LV dP/dt (mm Hg·sec^{-1})	2,229 (620)	1,936 (539)	N.S.	2,231 (752)	1,694 (616)	$P < 0.005$
LV(dP/dt)/DP (sec^{-1})	37.7 (4.5)	39.2 (5.8)	N.S.	41.5 (7.2)	37.5 (5.0)	$P < 0.05$
Peak aortic blood flow (ml·sec^{-1})	109 (32)	117 (31)	N.S.	121 (36)	99 (42)	N.S.
Aortic blood flow acceleration (ml·sec^{-2})	3,475 (1,088)	3,693 (1,517)	N.S.	3,895 (1,484)	2,890 (1,293)	$P < 0.025$
Peak LV power (milli-watts)	1,450 (374)	1,854 (639)	N.S.	1,735 (641)	1,592 (598)	N.S.
LV minute work (joules)	16.0 (6.7)	20.8 (10.0)	N.S.	20.4 (7.8)	17.1 (7.7)	$P < 0.05$
LV stroke work (milli-joules)	127 (44)	174 (63)	N.S.	150 (39)	146 (52)	N.S.

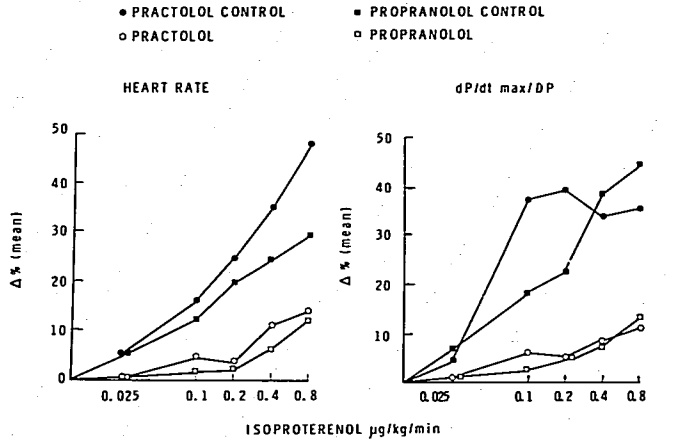


FIG. 2. Dose–response curves (chronotropic and inotropic) for infusion of isoproterenol before and after beta-receptor blockade with practolol or propranolol. The curves are based on mean values from all the dogs studied. SD have been omitted for clarity.

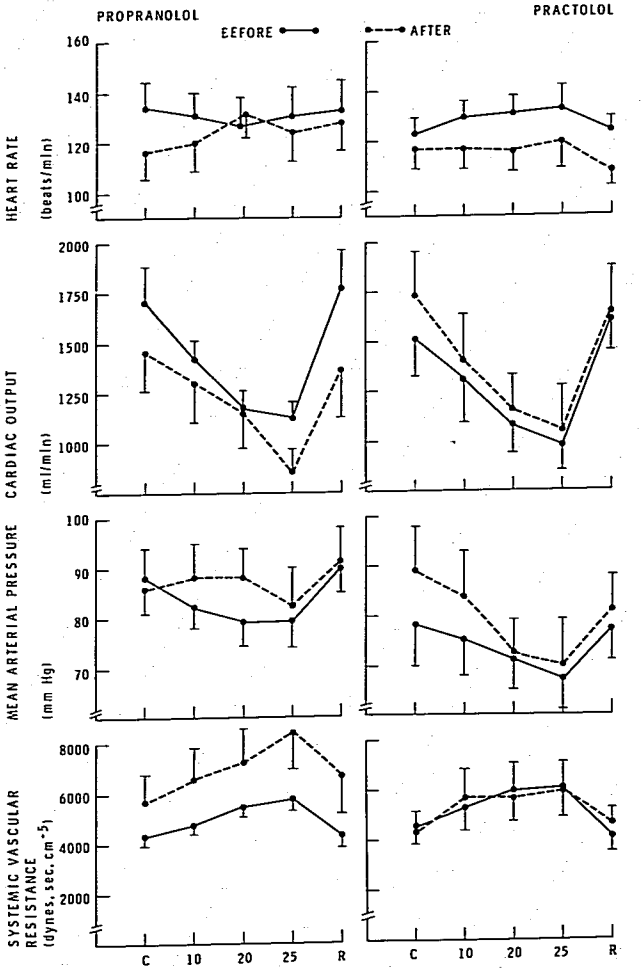
thesia are summarized in figures 3 and 4. All dogs tolerated this amount of hemorrhage well, both before and after beta-receptor blockade, but there were important differences between the responses before and after beta-receptor blockade, and between the groups treated with practolol and with propranolol.

There was no significant change of heart rate, in response to hemorrhage, either before or after either practolol or propranolol. Mean arterial pressure fell progressively in response to the graded hemorrhage in both groups of unblocked dogs, and returned to control levels rapidly in response to restoration of removed blood. Dogs receiving practolol had higher MAP's before bleeding commenced, but the values following 25 per cent blood loss were similar in blocked and unblocked animals. The blood pressure response to hemorrhage in the animals treated with propranolol was quite different, since MAP fell below the pre-bleeding control value only at the 25 per cent blood loss level (−5 per cent, not significant), while MAP after restoration of removed blood was 10 per cent higher than the pre-bleeding control value ($P < 0.05$).

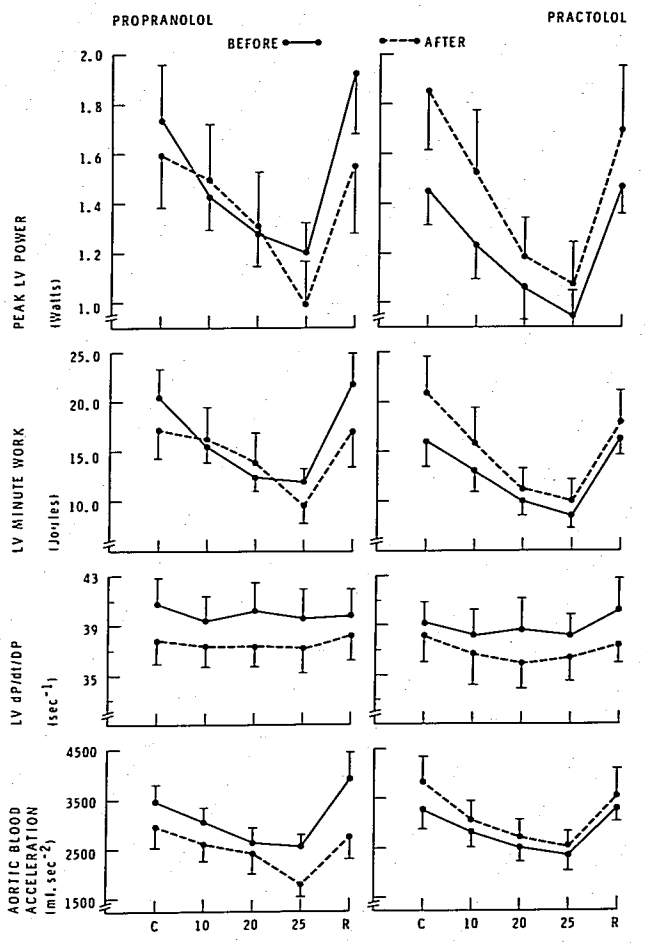
Cardiac output (and stroke volume) decreased progressively during hemorrhage, by 35 per cent ($P < 0.005$) after 25 per cent blood volume loss in both untreated groups, 38 per cent ($P < 0.001$) in practolol-treated animals, and 44 per cent ($P < 0.025$) in propranolol-treated animals. These changes were related to significant reductions ($P < 0.001$) of LVEDP under all the conditions of study. There was no significant difference between values at comparable stages of blood volume loss in the propranolol-treated compared with the practolol-treated animals.

The changes in SVR before and after practolol were similar, there being a progressive and significant increase with each incremental reduction of blood volume. The values of SVR in the propranolol-treated dogs were higher at each stage than those in the other animals, but the difference did not reach statistical significance.

Indices of left ventricular function and contractility showed little difference between the two groups of untreated dogs, nor between those treated with practolol and those treated with propranolol. Peak LV power and LV minute work were significantly decreased in



FIGS. 3 (*left*) and 4 (*right*). Hemodynamic responses to graded blood loss and subsequent replacement during halothane anesthesia before and after beta-receptor blockade with propranolol (*left* panels) or practolol (*right* panels). The stages (abscissa) are denoted by



C, control; 10, 20, and 25, values observed after withdrawal of 10, 20, and 25 per cent, respectively, of estimated blood volume; R, values observed after replacement of withdrawn blood.

TABLE 4. Changes in Oxygen Transport before and after Loss of 25 Per Cent of Blood Volume in Untreated and Beta-receptor-blocked Dogs (Means and SD)

	Untreated (n = 8)	Propranolol (n = 8)	Untreated (n = 7)	Practolol (n = 7)
$P\bar{v}_{O_2}$ (mm Hg)				
Control	49.6 (10.5)	46.7 (14.3)	50.1 (4.1)	54.5 (5.0)
After 25 per cent loss	40.5 (11.5)‡	38.2 (13.5)‡	39.3 (4.8)‡	41.4 (7.2)‡
$Ca_{O_2} - C\bar{v}_{O_2}$ (ml/100 ml STPD)				
Control	3.9 (1.5)	4.6 (2.6)	4.0 (1.3)	3.6 (0.6)
After 25 per cent loss	6.0 (2.7)‡	6.8 (3.2)*	6.3 (2.0)†	5.1 (2.2) NS
$\dot{V}_{O_2}$ (ml·min^{-1}/kg)				
Control	6.0 (1.2)	6.0 (2.0)	4.7 (1.4)	4.8 (0.9)
After 25 per cent loss	6.1 (2.1) NS	5.0 (2.0) NS	4.8 (1.1) NS	4.2 (0.9) NS

* $P < 0.05$ compared with control value.
† $P < 0.01$ compared with control value.
‡ $P < 0.001$ compared with control value.

all animals after 25 per cent blood volume loss, but the progressive reductions of both variables after 10 and 20 per cent blood losses were significant in the propranolol- and practolol-treated animals only ($P < 0.01$ or better). Peak acceleration of blood flow in the aorta followed the same pattern of changes as those of peak LV power and LV minute work, the changes being highly significant ($P < 0.001$) after 25 per cent blood volume loss in both untreated and beta-receptor-blocked animals. There was no significant difference between the values of LV minute work or peak LV power before and after either beta-receptor blocker at any stage during the bleeding protocol. Max LV (dP/dt)/DP showed no significant change in response to blood loss in either untreated or beta-receptor-blocked animals.

Pa_{O_2} was maintained at 147 mm Hg (SD 30) throughout the study in the practolol group, and at 166 mm Hg (SD 10) in the propranolol group. Pa_{CO_2}'s were 38.1 mm Hg (SD 4.4) and 42.7 mm Hg (SD 3.9), respectively. In both groups of animals, there were moderate but statistically insignificant reductions of both arterial blood *p*H and mixed venous blood *p*H in response to loss of 25 per cent of blood volume, both before and after beta-receptor blockade. Mixed venous blood P_{O_2} and O_2 content decreased significantly after 25 per cent blood loss, reflecting similar reductions of cardiac output in untreated and in beta-receptor-blocked animals (table 4), since there was no significant change of oxygen uptake.

Discussion

These studies showed that dogs with recently induced myocardial infarctions tolerated well the induction and maintenance of stable anesthesia, and the graded withdrawal and subsequent replacement of 25 per cent of their estimated blood volumes, both before and after beta-receptor blockade. At no time was there any indication that these interventions, or the added stresses induced by infusions of isoproterenol, phenylephrine or calcium gluconate, caused acute impairment of left ventricular performance to an extent that might cause progressive arterial hypotension leading to cardiac arrest. It is by no means clear to what extent this animal model is representative of the patient who has myocardial infarction superimposed upon chronic atherosclerotic disease. However, the results help to clarify the pharmacologic aspects of interactions between these two beta-receptor blockers and one anesthetic combination widely used in clinical anesthesia. The results also indicate that a heart whose performance has been impaired by recent infarction behaves like a normal heart in response to the specific interventions we studied.

In choosing halothane as the main anes-

thetic agent for this study, we were motivated to use not only an agent widely used in clinical practice, but also one whose cardiovascular pharmacology is well established. All gaseous, volatile and intravenously administered anesthetic agents cause reversible, dose-dependent impairment of myocardial contractility in isolated cardiac muscle preparations and in the hearts of intact animals. In the intact animal, such impairment of contractility implies that under the influence of an anesthetic, the myocardium is less able to develop power, thus stroke volume and cardiac output must be decreased unless the impedance to left ventricular ejection is simultaneously reduced.[20,26,27] Some anesthetics, such as diethyl ether and fluroxene, exert minimal depressant effects on myocardial contractility, and cause reduction of systemic vascular resistance; consequently, stroke volume and cardiac output are well maintained.[28–30] By contrast, halothane markedly impairs myocardial contractility, but has little effect on the overall impedance to left ventricular ejection[31]; thus, marked diminution of stroke volume, cardiac output, and arterial pressure characterizes halothane anesthesia in experimental animals and man. In equipotent doses, no other commonly used agent causes significantly more myocardial depression than halothane; thus, the lack of any additive effect of this agent with beta-receptor blocking drugs in this group of dogs with myocardial infarction is notable, and confirms the results of previous studies in dogs with normal heart function.[25,32]

The extent of myocardial infarction observed at autopsy, and the functional impairment of cardiac function reflected in the values of LV dP/dt, aortic blood flow acceleration, and cardiac output, serve to indicate that these dogs had limited functional cardiac reserve compared with normal dogs. The initial circulatory effects associated with induction and maintenance of anesthesia (table 2) support this contention. However, the responses of these animals, both before and after beta-receptor blockade, to either a reduction (acetylcholine) or an increase (phenylephrine) in systemic vascular resistance compared favorably with the responses of normal dogs to the same stresses.[25] Nevertheless, the responses to calcium gluconate, a specific non-adrenergic myocardial stimulant, indicated that following either practolol or propranolol there was slight impairment of the ability of calcium to increase myocardial contractility.

There were differences between the effects of practolol and propranolol that may be attributed to known differences between the actions of these drugs: 1) Practolol has intrinsic sympathomimetic activity, whereas propranolol does not.[33] 2) Practolol has a specific affinity for cardiac receptors, while propranolol has a greater affinity for peripheral vascular and other receptors.[34–35] 3) Propranolol is more effective in decreasing the maximum rate of depolarization (quinidine-like effect) of cardiac muscle.[36]

We attribute the fact that values of mean arterial pressure, cardiac output, aortic blood flow acceleration, peak LV power, and LV minute work were all higher after practolol administration to the effect of this drug in exerting moderate intrinsic sympathomimetic activity. This effect has also been observed after administration of practolol to patients anesthetized with halothane and nitrous oxide.[1] By contrast, propranolol did not have these effects, in that cardiac output, heart rate, aortic blood flow acceleration, peak LV power, and LV minute work were all decreased following its administration. In this respect, the responses of these dogs with myocardial infarction differed from those of normal animals under otherwise similar conditions.[25,32] On the one hand, these findings may be taken to imply that practolol may be more beneficial than propranolol in the management of patients with ischemic heart disease who need anesthesia, but on the other hand, it is clear that the myocardial depression induced in these animals by propranolol is probably not enough to warrant the suggestion that it is reasonable to withdraw the drug from patients prior to anesthesia and operation. The studies of Roberts *et al.*[25] of dogs pretreated for three weeks with propranolol (20 mg/kg/day) indicate that these animals tolerated halothane anesthesia, in incremental multiples of MAC, from 1.0 to 2.5, as well as did animals not

treated with propranolol. It is probable that the slight myocardial depression observed after intravenous administration of propranolol (in much higher doses than would be used clinically) is characteristic of this group of animals with recently induced myocardial infarction only. Our findings do not provide evidence for or against the use of beta-receptor blockers during anesthesia in man, nor do they indicate whether patients receiving beta-receptor blockers for the treatment of ischemic heart disease or hypertension should receive these drugs up to and during operation. Our results do indicate, however, that the combination of halothane–nitrous oxide anesthesia and beta-receptor blockade with either practolol or propranolol is not characterized by extreme impairment of cardiovascular function even in this group of animals. There was no evidence that beta-receptor blockade impaired the ability of the heart to react normally to changes in ventricular ejection loading, nor was there any serious failure of the heart to respond to a positive inotropic stimulus.

The influence of beta-receptor blockade on the cardiovascular response to hemorrhage is clearly much less than has been predicted; although there were major hemodynamic changes in response to withdrawal of 25 per cent of the dogs' estimated blood volumes, these changes were not significantly greater following administration of either practolol or propranolol. Similar responses to the same blood loss were found in dogs with normal hearts pretreated with high doses of propranolol during halothane anesthesia,[25] whereas cardiac outputs were reduced to dangerously low levels following the same amount of hemorrhage in beta-receptor-blocked animals anesthetized with trichloroethylene[37] or methoxyflurane.[38] This blood loss would be equivalent to a loss of about 1,500 ml in a 70-kg man, a greater loss than would normally be tolerated without volume replacement under the conditions of elective surgery. It would seem unlikely that human patients would behave qualitatively differently from these dogs, and we would predict that patients receiving beta-receptor blockers would respond to hemorrhage during anesthesia in much the same way as the dogs. It is notable that hemorrhage did not induce a significant increase in heart rate during anesthesia either before or after induction of beta-receptor blockade. This lack of a chronotropic response to hemorrhage has also been found in dogs with normal hearts anesthetized with halothane,[25] trichloroethylene,[37] and methoxyflurane.[38]

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