THE EFFECT OF BETA-ADRENERGIC BLOCKADE ON MYOCARDIAL HAEMODYNAMICS AND METABOLISM DURING LIGHT HALOTHANE ANAESTHESIA

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VENTRICULAR ARRHYTHMIAS during halothane anaesthesia have continued to be troublesome to the clinician. Although alteration of ventilation or anaesthetic depth will frequently abolish such arrhythmias, drug therapy is occasionally necessary. In view of the demonstrated association between adrenergic stimulation of the heart and ventricular irritability,[1] the use of the recently introduced beta-adrenergic blocking drug propranolol (Inderal) seemed a reasonable approach to the management of ventricular arrhythmias during halothane anaesthesia. The effectiveness of the drug has been amply demonstrated.[2–5] Only Johnstone has made an effort to evaluate the other major cardiac effect of beta-adrenergic blockade, which is inhibition of the force of myocardial contraction.[2] His technique of digital plethysmography has questionable validity, however. Craythorne has compared the effect of propranolol on the haemodynamics of cyclopropane and halothane in the dog, but he did not look into metabolism or oxygenation.[6] There is some evidence that beta blockade decreases myocardial blood flow,[7,8] and this aspect in association with anaesthesia has not been investigated at all. In order to evaluate the effects of propranolol on the heart lightly anaesthetized with halothane, a study of myocardial dynamics and substrate and oxygen kinetics was carried out in the intact dog heart *in situ*.

METHODS

Eight healthy male mongrel dogs weighing 20–25 kg were fasted overnight and brought to the laboratory unpremedicated. Anaesthesia was induced and the trachea was intubated with a cuffed tube with the aid of a single intravenous injection of thiopental (20 mg/kg) or thiopental (10 mg/kg) and succinylcholine (1 mg/kg). An oesophageal thermistor was passed to the level of the left atrium and temperature was maintained by external heating. Ventilation was controlled using a Bird Mark IV Ventilator with 100 per cent oxygen and halothane vaporized by a calibrated Fluotec Mark II Vaporizer. Mixed expired halothane concentration was monitored with an ultraviolet analyser. Physiological saline was infused throughout the procedure at a rate of approximately 100 ml/hr to assure adequate hydration.

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Catheters were introduced through femoral arterial cutdowns into the abdominal aorta and left ventricle and through jugular venous cutdowns into the right atrium and coronary sinus with fluoroscopic guidance. Right atrial, left ventricular and aortic pressures were recorded on a Sanborn polygraph through appropriate Statham transducers. The maximum rate of rise of the left ventricular pressure pulse (dp/dt) was differentiated electronically and recorded along with the electrocardiogram. Ventilation was adjusted to produce normal arterial blood gases. The halothane concentration was set as low as would keep the animal from moving or breathing against the ventilator (a rough minimal alveolar concentration) and the animal was allowed to stabilize for 30 to 60 minutes.

At this time cardiac output was determined in duplicate by the cardiogreen dye dilution technique with injection into the right atrium and withdrawal from the aorta. A Sanborn 130 Cardiac Output Computer was used for the readout. Myocardial blood flow was estimated from the coronary sinus washout of the radioisotope krypton[85] according to the method of Cohen *et al.*[9] Simultaneous aortic and coronary venous samples were collected for the determination of oxygen content, P_{O_2}, pH, P_{CO_2}, glucose, non-esterified fatty acids (NEFA), lactate, and pyruvate. The blood for the gas measurements was collected anaerobically in heparinized syringes and iced immediately. The samples for the lactate and pyruvate determinations were deproteinized within 30 seconds and centrifuged. Specimens for the glucose and NEFA estimates were centrifuged immediately, and the plasma was drawn off and iced. Blood sampling loss was replaced by blood drawn previously from the same dog. To document the beta adrenergic blockade, the animal's haemodynamic response to isoproterenol (0.1 μg/kg) was tested, propranolol (0.25 mg/kg) was injected intravenously, and, after ten minutes, the response to the same isoproterenol dose was again checked. In all cases the response to this dose of isoproterenol was blocked. As soon as ventilatory and circulatory stabilization had occurred, the protocol was repeated. Terminally the animals were sacrificed and the catheter placement was verified.

The blood gas tensions were measured on conventional electrodes, and the oxygen contents were determined by the Van Slyke manometric technique.[10] Glucose was analysed by the glucose oxidase method (Worthington Corp.), NEFA according to the colorimetric method of Duncombe,[11] and lactate and pyruvate by the enzymatic methods of Hohorst[12] (Sigma Corp.). Left ventricular stroke work and peripheral vascular resistance were calculated using standard formulae.[13,14] Statistical analysis was done with Student's *t*-test for paired samples.[15]

Results

At a mean expired halothane concentration of 0.69 per cent, the control myocardial dynamics and the changes induced by propranolol can be seen in Table I and Figures 1, 2, 3, and 4. Although cardiac output and left ventricular stroke work fell significantly, left ventricular dp/dt, heart rate, myocardial blood flow, and right atrial pressure did not change, while mean aortic pressure, peripheral

TABLE I

MYOCARDIAL DYNAMICS

	Control	Propranolol (0.25 mg/kg)	p
Heart rate (min)	116.00±7.26	106.00±7.98	
Rt. atrial pressure (mm Hg)	4.56±0.91	4.88±0.59	
L. ventricle end diastolic pressure (mm Hg)	6.50±0.94	10.31±2.06	<0.05
Mean aortic pressure (mm Hg)	112.90±3.68	120.13±3.68	<0.01
L. ventricle dp/dt	18.25±1.77	16.56±1.47	
Cardiac output (L/min)	2.13±0.28	1.66±0.24	<0.01
L. ventricle stroke work (gm metres)	34.37±4.22	30.14±3.78	<0.05
Peripheral vascular resistance	2.58±0.20	3.78±0.54	<0.05
Myocardial blood flow (cc/100 gm/min)	37.06±2.97	35.53±3.20	

N = 8; ± = standard error of the mean.

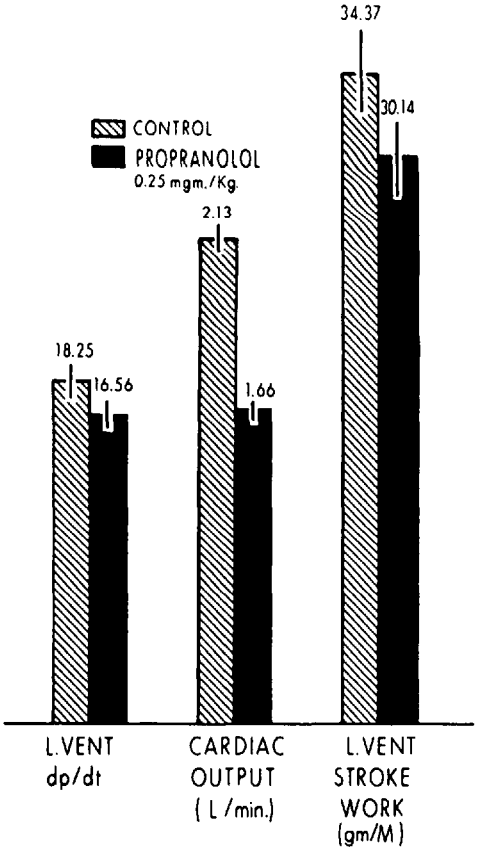

FIGURE 1. The effect of beta-adrenergic blockade on myocardial contractility.

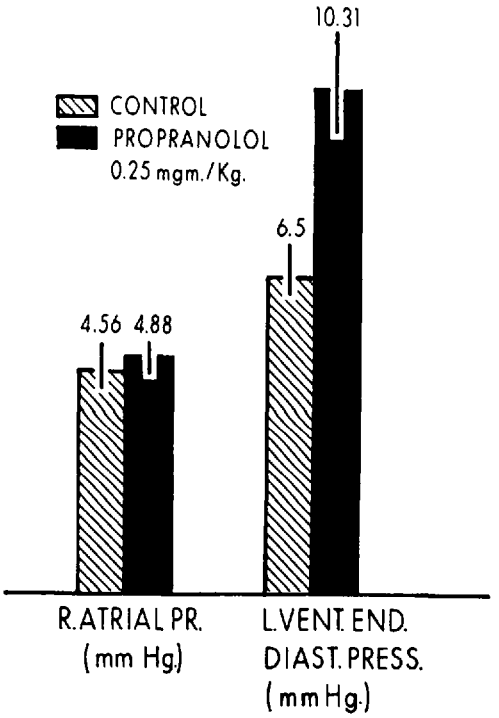

FIGURE 2. The effect of beta-adrenergic blockade on myocardial filling pressure.

vascular resistance, and left ventricular end diastolic pressure rose. There was no significant difference in myocardial oxygen uptake and excess lactate (Table II). Although a decrease in glucose uptake can be seen in Table III, the difference was not significant and no substrate arterial level or uptake changed significantly. The rhythm remained sinus except for brief periods immediately after the beta adrenergic challenge in the control animals. There was no significant difference in arterial pH, P_{CO_2}, P_{O_2}, haematocrit or oesophageal temperature between the control and beta blocked animals.

TABLE II

MYOCARDIAL OXYGENATION

	Control	Propranolol (0.25 mg/kg)
Arterial O_2 content (vol %)	21.07±0.60	21.27±0.65
O_2 uptake (ml/100 gm/min)	5.68±0.45	5.36±0.58
Excess lactate (mg %)	−1.32±0.65	0.37±0.53

N = 8; ± = standard error of the mean.

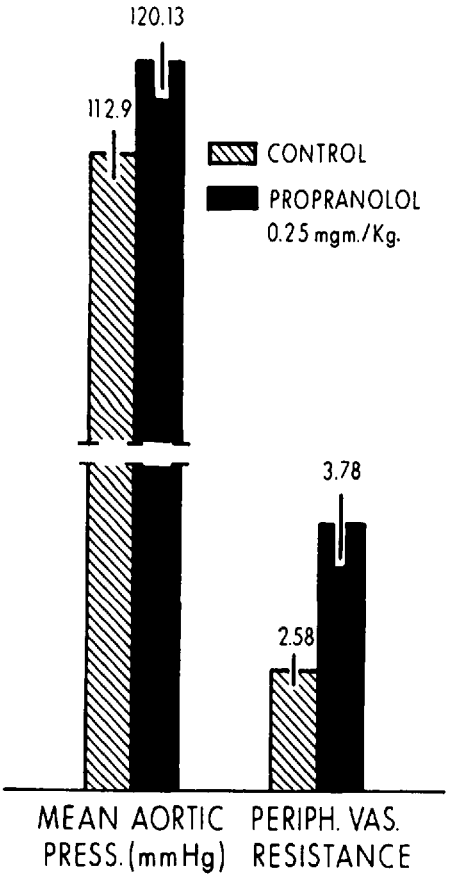

FIGURE 3. The effect of beta-adrenergic blockade on peripheral resistance.

TABLE III

SUBSTRATE KINETICS

	Control	Propranolol (0.25 mg/kg)
Glucose		
arterial level (mg%)	114.00±4.00	107.00±6.00
uptake (mg/100 gm/min)	4.84±1.73	1.67±0.84
Non-esterified fatty acids		
arterial level (μEq/L)	262.00±36	280.00±33
uptake (μEq/100 gm/min)	2.92±1.01	2.11±0.58
Lactate		
arterial level (mg%)	14.73±1.76	13.37±1.18
uptake (mg/100 gm/min)	3.18±0.56	3.26±0.49
Pyruvate		
arterial level (mg%)	1.59±0.08	1.37±0.10
uptake (mg/100 gm/min)	0.33±0.02	0.27±0.04

N = 8; ± = standard error of the mean.

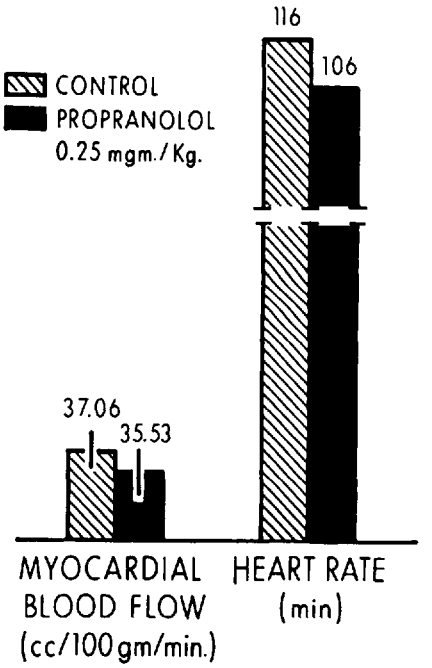

FIGURE 4. The effect of beta-adrenergic blockade on myocardial blood flow and heart rate.

DISCUSSION

Craythorne[6] saw a marked decrease in cardiac output and myocardial contractility and an increase in peripheral vascular resistance in dogs anaesthetized with 20 per cent cyclopropane and given 0.2 mg/kg propranolol. Jorfeldt[16] likewise saw marked circulatory depression with propranolol in humans under ether anaesthesia. The previously published work on halothane reveals no evidence of endogenous catechol release in the whole animal,[17] so that theoretically beta-adrenergic blockade should not produce such deleterious effects. Indeed, in the same study reported above, Craythorne[6] saw only a 10 per cent decrease in heart rate and no other cardiodynamic changes with 1 per cent halothane and propranolol.

Although one of the indicators of myocardial contractility in this study, left ventricular dp/dt, did not change significantly with beta blockade, the decrease in cardiac output and consequently in left ventricular stroke work, in the face of an unchanged heart rate and increased left ventricular end diastolic pressure, can be interpreted as indicating myocardial depression. Wallace *et al.*[18] have shown that the preload (left ventricular end diastolic pressure) and the after-load (mean aortic pressure) can modify left ventricular dp/dt in conditions of changing myocardial contractility. The increase in left ventricular end diastolic pressure and mean aortic pressure seen here could have obscured a fall

in left ventricular dp/dt caused by a negative inotropic effect. The increased aortic pressure also served to maintain myocardial blood flow in this circumstance. Although propranolol is known to have a direct depressant effect on the myocardium, this occurs with much larger doses than were used in this study,[19–21] so that the effect seen here is presumed to be a beta-adrenergic blocking effect.

The increased peripheral vascular resistance indicates vasoconstriction. This is not usually considered to be a property of beta-adrenergic blockade. There are two possible mechanisms for this phenomenon in association with light halothane anaesthesia: (1) Although it has not been demonstrated objectively, it seems probable that there is some endogenous catecholamine output under light halothane.[1] In this circumstance, blockade of the peripheral beta-adrenergic vasodilation would leave the alpha mediated vasoconstriction unopposed. (2) Light halothane anaesthesia produces peripheral vasodilation.[17] Klide *et al.* have shown that the smooth muscle relaxation produced by halothane in the tracheobronchial tree and the uterus is beta-adrenergically mediated.[22,23] It would seem logical to suppose that the vascular smooth muscle relaxation produced by halothane was also mediated in this fashion, in which case the increase in peripheral vascular resistance seen in this study could be explained by an inhibition of the peripheral vasodilation produced by halothane.

There are several differences from the other study of the effect of propranolol on haemodynamics with halothane, which could explain the different results.[6] The effects of surgery and an open chest and pericardium must be taken into account in Craythorne's study. The level of halothane (1% inspired) was probably slightly deeper, although no blood or gas measurements are provided. The cardiodynamic and myocardial metabolic effects of high halothane concentrations[24,25] resemble those seen with beta-adrenergic blockade,[14,20,21] so that deeper halothane anaesthesia might well obscure changes produced by propranolol.

The lack of myocardial excess lactate and the maintenance of oxygen and lactate uptake indicate adequate myocardial oxygenation.[26] Two other studies have shown a decrease in myocardial fatty acid uptake with beta-adrenergic blockade, producing myocardial depression.[21,27] In one there were decreases in lactate and pyruvate uptake as well. In this study, no change in arterial level or myocardial uptake of any substrate could be shown. This may be related to the smaller dose of propranolol used, in comparison with one study,[25] or with the use of halothane rather than the basal anaesthetics used in the other.[21]

The overall effect of beta-adrenergic blockade on the canine heart during light halothane anaesthesia does not appear to be severely depressant, but it seems likely that the maintenance of arterial blood pressure in the face of decreased cardiac output might provide a false sense of security. Indeed, in the presence of hypovolaemia, endogenous catechol depletion (reserpine), or a diseased heart, this adaptation might not be so efficient. Consequently, the conclusions reached by Johnstone seem reasonable. He felt that the combination of propranolol and light halothane anaesthesia was relatively safe in the "fit, normovolaemic patient."[2] It is also of considerable interest that he found it necessary to combine atropine with the propranolol in order to prevent brady-

cardia and hypotension from occurring in man. This may be a reflection of species variation, for no such effect was seen in this study.

Summary

The effect of beta-adrenergic blockade produced by propranolol (0.25 mg/kg) on myocardial haemodynamics and metabolism was investigated in eight closed-chest dogs lightly anaesthetized with halothane (0.69% expired). A significant decrease in cardiac output and left ventricular stroke work was seen, with increases in left ventricular end diastolic pressures, mean aortic pressure, and peripheral vascular resistance. There was no change in heart rate, right atrial pressure, or the rate of rise of left ventricular pressure (dp/dt). Myocardial blood flow, oxygen uptake, and excess lactate were likewise unchanged. There was no significant difference between the control and beta-blocked animals in the arterial levels or in regard to the myocardial uptake of glucose, non-esterified fatty acids, lactate, or pyruvate. It appeared that the myocardial depression produced by beta adrenergic blockade in these animals was offset by the increased peripheral vascular resistance and mean aortic blood pressure. It is suggested that were such compensation not possible, the effect of beta-adrenergic blockade in light halothane anaesthesia might be more deleterious.

Résumé

Sur huit chiens à thorax fermé, légèrement anesthésiés au fluothane (0.69% à l'expiration), on a cherché l'effet d'un blocage adrénergique bêta sur l'hémodynamique et le métabolisme myocardique. On a observé une diminution importante du débit cardiaque et du travail de la systole ventriculaire gauche, avec une augmentation des pressions ventriculaire gauche et diastolique, de la pression aortique moyenne et de la résistance vasculaire périphérique. Il n'y a pas eu de changement du rythme cardiaque, de la pression auriculaire droite ou du taux d'élévation de la pression ventriculaire gauche (dp/dt). Le courant sanguin du myocarde, la consommation d'oxygène et le lactate sont demeurés inchangés. Il n'y a pas eu de différence importante entre les animaux de contrôle et les animaux soumis au blocage bêta quant au niveau artériel ou à la consommation myocardique du glucose, des acides gras, du lactate ou du pyruvate. Il a semblé que la dépression myocardique produite chez ces animaux par le blocage adrénergique bêta était causée par la résistance vasculaire périphérique augmentée et par l'élévation de la pression sanguine aortique moyenne. On suppose que si une telle compensation n'était pas possible, l'effet du blocage adrénergique bêta sous anesthésie légère au fluothane pourrait être plus nocive.

Acknowledgments

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