HAEMODYNAMIC INTERACTIONS OF HIGH-DOSE PROPRANOLOL PRETREATMENT AND ANAESTHESIA IN THE DOG II: THE EFFECTS OF ACUTE ARTERIAL HYPOXAEAMIA AT INCREASING DEPTHS OF HALOTHANE ANAESTHESIA

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SUMMARY
Beta-adrenergic blockade may impair the normal cardiovascular response to hypoxia occurring during general anaesthesia. The haemodynamic effects of acute hypoxia, induced by a 90-s period of ventilation with nitrogen, were studied during increasing depths of halothane anaesthesia up to a maximum of 2.5% inspired halothane in dogs chronically implanted with intracardiac catheters, a left-ventricular pressure transducer and an aortic blood flow transducer. An untreated group of dogs and a group which had been treated for 3 weeks with propranolol 20 mg/kg/day were compared. The beta-blocked group had lesser cardiac output values, left-ventricular contractility indices, external left-ventricular work and peak left-ventricular power at all depths of anaesthesia except 2.5% halothane, but both groups responded to hypoxia similarly at each depth of anaesthesia. Cardiac performance was enhanced in both groups during acute hypoxia. No adverse haemodynamic effect of the combination of propranolol, halothane and hypoxia was demonstrated.

Concern has been expressed that beta-adrenergic blockade might obtund the normal responses of the cardiovascular system to arterial hypoxaemia occurring during general anaesthesia, thus preventing the anaesthetist from diagnosing the hypoxic state (Johnstone, 1966; Krasnow and Barbarosh, 1968; Katz and Bigger, 1970). Thus accidental hypoxia, occurring during anaesthesia, might prove fatal much more rapidly in the presence of beta-blockade than if sympathetic function were unimpaired. However, there is little firm evidence to substantiate this view. Short periods of hypoxia, sufficiently severe to cause cyanosis, may occur during anaesthesia as a result of airway obstruction, the accidental disconnection of a paralysed patient from a ventilator, and ventilator failure. The hypoxia is usually recognized rapidly, the cause is corrected and the patient suffers no permanent ill-effects. We have investigated the effect of high-grade beta-adrenergic blockade with propranolol on the haemodynamic response to this form of hypoxia using the dog anaesthetized with halothane as the experimental model. It has been shown that deeper levels of halothane anaesthesia greatly increase the mortality of longer-term hypoxia in dogs (Cullen and Eger, 1970; Nisbet et al., 1972), and our studies of short-term hypoxia were conducted at various depths of anaesthesia between 1% and 2.5% inspired halothane.

METHODS
The experiments were performed in conjunction with halothane dose-response studies which have been described previously (Roberts et al., 1976). Seven healthy mongrel dogs (mean weight 13.6 kg) which had been treated with propranolol 20 mg/kg/day for 3 weeks, and a control group of five untreated dogs (mean weight 12.6 kg) were studied. The details of the operative procedure, the calibration and recording of haemodynamic variables, blood-gas measurements as well as the computations and data analysis have also been fully described (Roberts et al., 1976). The full daily dose of propranolol (20 mg/kg) was administered by mouth 2 h before the induction of anaesthesia.

When a steady state of anaesthesia had been achieved after 90 min normocapnic IPPV with 1% halothane in oxygen, blood-gas and haemodynamic measurements were made. Acute arterial hypoxaemia was induced by changing the inspired gas mixture to 1% halothane in “White Spot” nitrogen and continuing IPPV on an open circuit system for 90 s. The dog was then disconnected, apnoeic, from the ventilator, arterial and mixed venous blood was sampled and cardiovascular measurements were recorded over a 10-s period. The composition of the inspired gas was then changed to halothane in oxygen, and IPPV was recommenced. The inspired halothane
concentration was increased by increments of 0.5% up to 2.5% at 20-min intervals. At the end of each 20-min period, control haemodynamic recordings were taken and the response to nitrogen ventilation, as described above, was noted. The animals were then ventilated with oxygen for 5 min and this was followed by a further period of 40 min of anaesthesia with 1% halothane. Cardiovascular variables and the blood-gas status were reassessed in order to demonstrate that deterioration of the preparation had not occurred during the course of the study.

RESULTS

Blood-gas and acid-base variables

Arterial $P_{O_2}$ in the untreated group decreased from a mean value of 358 mm Hg (SD 52 mm Hg) during ventilation with 1% halothane in oxygen to 31 mm Hg (SD 5 mm Hg) after 90 s ventilation with 1% halothane in nitrogen. This caused a decrease in mean $S_{O_2}$ from 99.9% to 53%. Under the same experimental conditions the propranolol-treated group had a decrease in $P_{O_2}$ from 324 mm Hg (SD 103 mm Hg) to 30 mm Hg (SD 6 mm Hg), causing a reduction in $S_{O_2}$ from 99.9% to 51%. Arterial pH decreased from 7.382 to 7.377 as a result of hypoxia in the untreated group, and from 7.380 to 7.376 in beta-blocked dogs. Mean $P_{CO_2}$ decreased by 3 mm Hg in the untreated animals and by 4 mm Hg in the beta-blocked dogs. Statistical analysis showed that there were no significant differences in these responses between the untreated and treated groups. Thus the haemodynamic effects of the hypoxic stimulus in the two groups could be validly compared. Statistical analysis of blood-gas and acid-base variables at each of the other inspired halothane concentrations showed that changes in $P_{O_2}$, $P_{CO_2}$ and pH similar to those observed during 1% halothane anaesthesia occurred in both groups during hypoxia.

Haemodynamic variables

The effects of hypoxia on measured and derived cardiovascular variables are shown in figures 1, 2, 3 and 4. Typical recorded responses are shown in figure 5. Percentage changes in any variable refer to alterations from the control values which were measured just before hypoxia was induced.

The heart rate increased slightly during hypoxia in both groups at all inspired halothane concentrations. These increases ranged from 4% to 6% and were not statistically significant. The systolic arterial pressure increased slightly during hypoxia in both groups at all depths of halothane anaesthesia. The increases ranged from 4% to 12% and tended to be greater at the lower halothane concentrations in the presence of beta-blockade. Only at the 2.5% halothane level in propranolol-treated dogs was the increase statistically significant. The diastolic arterial pressure decreased slightly (range $-1\%$ to $-6\%$) in untreated animals during hypoxia, while tending to increase in the beta-blocked group (range $-1\%$ to $11\%$). These changes resulted generally in a small increase in the mean arterial pressure (up to $11\%$) with the greatest increases occurring in the propranolol-treated group. None of these changes was statistically significant. Left-ventricular end-diastolic pressure (LVEDP) values were similar in untreated and beta-blocked dogs at each halothane concentration both before and after hypoxia, although LVEDP increased slightly above the control values with increasing depths of anaesthesia in both groups. There was no significant difference between the two groups in the responses of these intravascular pressures to hypoxia.
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Cardiac output increased similarly in both groups at all depths of anaesthesia as a result of hypoxia. The increases ranged from 9% to 26%, these changes being significant except at the 2.5% inspired halothane level. Increases in cardiac output were achieved mainly by increases in stroke volume while a change in heart rate played a minor role. Systemic vascular resistance decreased during hypoxia in both groups at all stages (range -3% to -22%) with the largest changes occurring in untreated dogs. However, these changes were not statistically significant and there was no significant difference between the responses of the two groups.

Myocardial contractility indices. The maximum rate of increase of left-ventricular pressure (LV dP/dt max) increased during hypoxia in both groups at all inspired halothane concentrations, by 26% to 56%. The normalized index, dP/dt max divided by instantaneously developed pressure (LV dP/dt max/IP), was also increased (12% to 28%) as was the maximum acceleration of aortic blood flow (dQ/dt max), this last index being increased by 12% to 39%. The increases in all three indices as a result of hypoxia were statistically significant except at the 2.5% halothane level, and were similar in both groups.

External left-ventricular stroke work (LVSW), external minute work (LVMW) and peak left-ventricular power (PLVP) all increased from the control values in both groups of dogs at all depths of anaesthesia as a result of the hypoxic stimulus (fig. 4). LVSW was increased by 17% to 22% in the untreated dogs while increases of 7% to 29% were observed in the beta-blocked group at the various depths of anaesthesia. Similarly, LVMW increased by 18% to 28% in untreated dogs and by 14% to 34% in treated animals. PLVP increased by 24% to 31% in the untreated group and by 20% to 35% in the treated group. In general, all these changes were statistically significant in both groups except at the 2.5% halothane level, while the responses of the two groups did not differ significantly at any experimental stage.

**DISCUSSION**

A large amount of experimental evidence relating to the cardiovascular effects of medium- and long-term
hypoxia is available. Many workers have sought to define the mechanisms whereby cardiac output is enhanced and oxygen transport maintained. Numerous studies have reported the effects of modification of sympathetic neural and humoral responses to hypoxia by surgical or pharmacological methods. The immediate response of the heart to severe hypoxia is mediated mainly by increased sympathetic neural activity. Woods and Richardson (1959) and Kahler, Goldblatt and Braunwald (1962) demonstrated that adrenalectomy alone did not impair the early cardiac response to severe hypoxia, while Greenfield and Ebert (1963) showed that cardiac denervation by the only totally reliable method, cardiac autotransplanta-

tion, completely inhibited the early response. Direct recording from cardiac sympathetic nerves showed very high levels of impulse traffic during severe hypoxia in cats (Downing, 1966) and in rabbits (Korner, Uther and White, 1969). The consensus of opinion is that the maintenance of enhanced cardiac performance during longer periods of moderately severe hypoxia is a function of catecholamines secreted by the adrenal medulla (Kontos and Lower, 1969; Chiong and Hatcher, 1972). The previous administration of beta-adrenergic drugs has been shown to reduce greatly the cardiovascular response to hypoxia (Hatcher and Jennings, 1966; Daugherty, Scott and Haddy, 1967; Krasney, 1967; Kontos and Lower, 1969). Malik and Langford-Kidd (1973), however, were unable to demonstrate any effect of propranolol 2.0 mg/kg i.v. on the heart rate and cardiac output increases observed in dogs anaesthetized with pentobarbitone, after 20 min at \( P_{a_O_2} \) 30 mm Hg.

Myocardial hypoxia, whether caused by a decrease in coronary blood flow or a reduction in arterial oxygen content, eventually results in depression of myocardial contractility (Tennant and Wiggers, 1935; Bing, 1965; Case, 1966; Ng, Levy and Degeest, 1966). Similar depression occurs in isolated cardiac muscle preparations during hypoxia (Tyberg et al., 1970; Henderson 1974; Nayler, 1974). However, there have been occasional reports of transient increases in contractility when heart preparations isolated from humoral influences were first subjected to hypoxia. Ng, Levy and Degeest (1966) showed that when heart rate was maintained constant by atrial pacing, perfusion of the coronary circulation of dogs with blood at \( P_{O_2} \) 40 mm Hg increased contractility, but that reduction of the \( P_{O_2} \) of the perfusing blood to 25 mm Hg resulted in cardiac depression. Cross and colleagues (1963) found that there was a transient increase in the spontaneous heart rate and contractility of the isolated, perfused dog heart when the coronary artery \( P_{O_2} \) was reduced to 25 mm Hg, but that depression ensued after 1 or 2 min. Krasney (1967) found that pretreatment of dogs with bretylium tosylate, which inhibits the release of noradrenaline from nerve terminals, plus the administration of propranolol 2–3 mg/kg did not prevent an increase in heart rate of 11–22 beat/min when open-chest dogs were subjected to hypoxia. He considered this to be a direct effect of hypoxia on the discharge rate of the sino-atrial node and a facilitation of conduction in the Purkinje system. Kübler (1974) found that glycolytic enzyme activities were similar in the canine and human heart and that the myocardial
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Fig. 5. Haemodynamic recordings to demonstrate the effects of acute arterial hypoxaemia during 1% halothane anaesthesia. Upper panel: untreated dog. Lower panel: dog pretreated with propranolol 20 mg/kg/day. Key: AoP = Aortic pressure; LVP = left ventricular pressure; LAP = left atrial pressure.
Responses of propranolol-treated animals to hypoxia blockade. Should this have been the case, the cardiac of sympathetic activity penetrating the receptor observed results were a result of a high level beta-blockade is never "complete", it is unlikely that not clear. While it is recognized that propranolol is a competitive beta-receptor blocking agent and that vascular performance during short-term hypoxia is known to increase the contractility of isolated cardiac muscle (Pannier and Bruetsaert, 1968; Pannier and Leusen, 1968; Foex, 1972).

We conclude from this study that transient severe hypoxia, under the experimental conditions stated, was no more dangerous in the presence of propranolol than in its absence. It must be stressed, however, that this conclusion relates only to the effects of transient hypoxia during halothane anaesthesia with normocapnia in dogs with normal cardiovascular systems. It may not be applicable in the presence of cardiovascular diseases—the commonest diseases for which beta-blocking drugs are given. The conclusion cannot be extrapolated to situations in which hypoxia is of longer duration, anaesthetic agents other than halothane are in use or large changes in arterial carbon dioxide tension from the normocapnic condition occur. Further studies will be required to evaluate the safety of beta-adrenergic blockade under these various conditions.

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REFERENCES


