THE INFLUENCE OF ARTERIAL pH CONTROL ON THE CARDIOTOXICITY OF ISOPRENALINE IN HYPOXIC DOGS

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When repeated doses of isoprenaline (2.5 µg/kg) were administered to hypoxic dogs (PaO_2 = 30-40 mmHg) a lethal response was obtained in 7.6 doses. In all five dogs, a common pattern of changes in PaO_2, $PaCO_2$, pH and B.E. (base excess) values emerged, namely a fall in PaO_2, pH and B.E. which became significant ($P<0.05$) after the second dose, and a rise in $PaCO_2$ which became significant after the fifth dose. The marked fall in pH and B.E. initially accompanied by little change in $PaCO_2$, indicated the creation of a metabolic acidosis, attributable to the combined acidotic effects of hypoxia and isoprenaline (Mc Cutcheon 1962; Mayer et al 1961). It was decided to repeat these experiments while maintaining arterial pH relatively constant in an attempt to evaluate the effects of acidosis on the cardiovascular response of hypoxic dogs to isoprenaline.

Using a modified Boyle's apparatus, PaO_2 values of 30-40 mmHg were produced in each artificially respired anaesthetized greyhound. Arterial blood samples were analysed for PaO_2, $PaCO_2$, pH and B.E. Blood pressure and heart rate were recorded on a Devices M 19 recorder. Animals were infused with M $NaHCO_3$ (0.1 ml/kg/min) or 0.3 M THAM (Trihydroxymethylaminomethane) (0.3 ml/kg/min). Doses of isoprenaline (2.5 µg/kg) were administered according to a pre-arranged time schedule. Four groups of experiments were performed differing in either the agent used to maintain pH or the length of infusion time prior to isoprenaline dosage (see Table 1).

Table 1.

Treatment	Infusion time (min) prior to isoprenaline administration	Mean increases in heart rate with each dose (beats/min)	Mean number of doses survived by each group	Pattern of death
$NaHCO_3$	60	26	6.8	VF
$NaHCO_3$	6	24	6.6	CD
THAM	60	25	13.0	CD
THAM	6	25	7.0	CD
Unbuffered	0	42	7.6	CD

Infusion of $NaHCO_3$ and THAM prevented the fall in pH and B.E. normally associated with the i.v. injection of isoprenaline during hypoxia. PaO_2 decreased with increasing number of doses and was accompanied by a continuous marked rise in $PaCO_2$ in those dogs infused with $NaHCO_3$ for one hour prior to dosing with isoprenaline. The mean PaO_2 value immediately before the fatal dose in those dogs pretreated for one hour with THAM was significantly lower than similar mean values for the other groups, although the mean PaO_2 values for each group after dose seven (see Table 1) were similar. Blood pressure decreases with each dose were of a similar magnitude in all pH-controlled groups and also in the group in which pH was not controlled. Mean heart rate increases and the pattern of death, cardiac depression (CD) or ventricular fibrillation (VF), for each group are shown in Table 1. Downing et al (1966) have shown that reduced myocardial contraction may result from the combined effects of acidosis and hypoxia. However, from the present experiments, it would appear that simply maintaining pH constant during administration of isoprenaline, (when an acidosis would be expected to develop), does not increase the number of doses of isoprenaline which hypoxic dogs can survive. The enhanced survival noted in those dogs pretreated with THAM for 60 min may perhaps be attributed to the latter effecting an intracellular as well as an extracellular alkalosis, since THAM penetrates the cell membrane (Holmdahl et al 1962).

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