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VENTILATORY RESPONSE TO CO2 REBREATHING AFTER
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ENVIRONMENTAL MEDICINE NATICK MA S E WEINBERGER ET AL.

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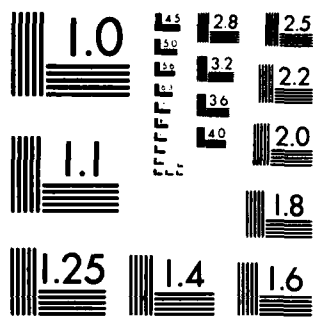
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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) Administration of adrenergic agonists enhances resting ventilation and increases responsiveness to CO₂ inhalation, though there are conflicting data about the effect of adrenergic blockade on ventilatory responses. In this study, we investigated the effect of alpha- or beta-adrenergic blockade on the ventilatory response to hyperoxic CO₂ rebreathing in awake goats. Five goats were studied before and after intravenous administration of phentolamine (3.8 mg bolus followed by 0.19 mg/min) or propranolol (0.15 mg/kg). Adequacy of alpha- or beta- adrenergic

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blockade was subsequently demonstrated by assessing the pressor response to norepinephrine or the heart rate response to isoproterenol, respectively. There was no difference (compared to control studies) in the mean slope, x-intercept, or ventilation at end-tidal $PCO_2 = 70$ torr for the CO_2 response curves after the goats had received either phentolamine or propranolol. When mean inspiratory flow rate (V_T/T_i) was plotted against end-tidal PCO_2 , there was also no change in slope, x-intercept, or V_T/T_i at end-tidal $PCO_2 = 70$ torr after the goats had received propranolol. Though there was a slight decrease in the slope and x-intercept after phentolamine administration, there was no change in V_T/T_i at end-tidal $PCO_2 = 70$ torr after phentolamine. We conclude that acute administration of alpha- or beta-adrenergic blockers does not affect ventilatory response to CO_2 inhalation in goats, and suggest that adrenergic activity is not an important modulating influence for CO_2 responsiveness in this species.

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VENTILATORY RESPONSE TO CO₂ REBREATHING AFTER ADRENERGIC
BLOCKADE IN GOATS

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Abstract

Administration of adrenergic agonists enhances resting ventilation and increases responsiveness to CO_2 inhalation, though there are conflicting data about the effect of adrenergic blockade on ventilatory responses. In this study, we investigated the effect of alpha- or beta-adrenergic blockade on the ventilatory response to hyperoxic CO_2 rebreathing in awake goats. Five goats were studied before and after intravenous administration of phentolamine (3.8 mg bolus followed by 0.19 mg/min) or propranolol (0.15 mg/kg). Adequacy of alpha- or beta- adrenergic blockade was subsequently demonstrated by assessing the pressor response to norepinephrine or the heart rate response to isoproterenol, respectively. There was no difference (compared to control studies) in the mean slope, x-intercept, or ventilation at end-tidal $P_{\text{CO}_2} = 70$ torr for the CO_2 response curves after the goats had received either phentolamine or propranolol. When mean inspiratory flow rate (V_T/T_i) was plotted against end-tidal P_{CO_2} , there was also no change in slope, x-intercept, or V_T/T_i at end-tidal $P_{\text{CO}_2} = 70$ torr after the goats had received propranolol. Though there was a slight decrease in the slope and x-intercept after phentolamine administration, there was no change in V_T/T_i at end-tidal $P_{\text{CO}_2} = 70$ torr after phentolamine. We conclude that acute administration of alpha- or beta-adrenergic blockers does not affect ventilatory response to CO_2 inhalation in goats, and suggest that adrenergic activity is not an important modulating influence for CO_2 responsiveness in this species.

Index terms

Ventilatory control, phentolamine, propranolol

Introduction

Breathing is influenced by a complex interaction of stimuli and modulating factors acting at various levels of the nervous system. These modulating factors include input from the cerebral cortex and presumably from neurohumoral (including hormonal) systems (4). There are two ways in which neurohumoral factors could exert an influence on ventilatory control. First, the baseline level of activity of the system at the time of testing could influence responsiveness to ventilatory stimuli, such as hypoxia or hypercapnia. Second, the ventilatory stimulus itself could affect activity of the neurohumoral system, thereby indirectly stimulating or inhibiting ventilation through a neurohumoral mechanism.

The sympathoadrenal system is one example of a neurohumoral system potentially capable of interacting with ventilatory control. Several studies using adrenergic agonists suggest that administration of these agents increases resting ventilation and may augment the response to acute hypoxia or hypercapnia (2, 5, 7, 8, 14-16). However, demonstration of an effect of exogenous adrenergic agonists on ventilation does not necessarily mean that intrinsic sympathoadrenal activity normally influences ventilatory responsiveness. To establish that possibility, one must either quantitate intrinsic sympathoadrenal activity, or assess the effect of adrenergic blockers on ventilatory responses.

Prior studies on the effect of adrenergic blockers on ventilatory control have produced conflicting results. Most of these studies have been done in humans. After a single dose of

the beta-blocker propranolol, the ventilatory response to CO₂ inhalation was reported to be either decreased (9,13) or unchanged (6,10). Similarly, conflicting results were observed after administration of propranolol for several days (1,6). In other studies, administration of an alpha adrenergic agonist did not affect basal minute ventilation in humans (5) or the response to hyperoxic CO₂ rebreathing in goats (3).

To explore further the possibility that the sympathoadrenal system normally plays a role in the regulation of breathing, we assessed the effect of alpha blockade with phentolamine or beta blockade with propranolol on the ventilatory responses of awake goats to CO₂ rebreathing.

Methods

Five adult goats (4 males, 1 female) weighing 31 to 58 kg (mean 38.4 kg) were used in all experiments; each animal was studied at rest in the awake, fasted state. All animals had previously been provided with skin-denervated carotid loops. For each study, two plastic cannulas were inserted percutaneously, one into the carotid artery and the other into the contralateral external jugular vein. The arterial cannula was connected to a pressure transducer for continuous monitoring of heart rate and arterial blood pressure, which were displayed on a Brush recorder (Gould model 200). The venous catheter was used for administration of drugs.

Respiratory Measurements

Carbon dioxide rebreathing was performed by a modification of the technique of Read (11). A latex rubber respiratory mask

was fitted snugly over the goat's snout and connected to a three-way Y valve through wide-bore tubing (30 cm length, 3.5 cm i.d., Warren E. Collins). One of the remaining ports of the valve was open to air; the other was connected to a rebreathing bag enclosed in a rigid box. The box was connected by wide-bore tubing (2 m length, 3.5 cm i.d.) to a Wedge spirometer (Med Science model 570). Gas was sampled continuously from the mask at a rate of 60 ml/min, and partial pressures of O₂ and CO₂ were measured with a mass spectrometer (Perkin-Elmer model 1100A). All measured variables were displayed on the strip-chart recorder and recorded on magnetic tape (Hewlett-Packard model 3968) for later analysis by computer.

Each rebreathing test was started with approximately 5 L of gas (7% CO₂, balance O₂) in the bag. When end-tidal PCO₂ (PETCO₂) had been stable for at least 2 minutes with the goat breathing air, the Y valve was turned at end-expiration so that the goat subsequently inspired from and expired into the rebreathing bag. Rebreathing was terminated when PETCO₂ reached approximately 75 torr or the goat became restless. Rebreathing tests were performed in triplicate on each goat for each experimental condition.

Experimental Design

Each goat was studied on separate occasions at least 48 hours apart. On each day, three baseline CO₂ rebreathing tests were performed at least five minutes apart prior to administration of an adrenergic blocker.

For studies involving alpha adrenergic blockade, phentolamine was administered intravenously with an initial

bolus of 3.8 mg followed by a continuous infusion of 0.19 mg/min throughout the duration of the rebreathing studies. The first of the three post-phentolamine rebreathing studies was started five minutes after the bolus was given. Following the final post-phentolamine rebreathing study and while phentolamine was still being infused, an intravenous infusion of norepinephrine (40 μ g/min) was administered to assess the effectiveness of alpha blockade in attenuating the pressor response to norepinephrine.

For studies involving beta adrenergic blockade, propranolol (0.15 mg/kg) was administered as a single intravenous infusion over 10 minutes after three control CO₂ rebreathing studies. The first of the three post-propranolol rebreathing studies was started 10 minutes after the infusion was completed. Following the final post-propranolol study, isoproterenol (2 μ g/min) was infused intravenously to test the adequacy of beta blockade in attenuating the heart rate response to isoproterenol. In separate studies, the same doses of norepinephrine and isoproterenol were administered intravenously to the goats to measure the effect of these adrenergic agonists on blood pressure and heart rate, respectively, in the absence of adrenergic blockers. Whenever norepinephrine or isoproterenol was infused, blood pressure and heart rate measurements were continuously recorded, and the values obtained after five minutes of infusion were used for data analysis.

Data Analysis

For each CO₂ rebreathing curve, minute ventilation ($\dot{V}_E$), tidal volume (VT), inspiratory time (Ti), and mean inspiratory

flow ($\dot{V}_T/T_i$) were derived on a breath-by-breath basis. All volume data were expressed at BTPS conditions. Data obtained from the triplicate rebreathing studies performed under a particular experimental condition in each goat were pooled for plotting and statistical analysis (Figure 1). Linear regressions were calculated for plots of $\dot{V}_E$ and $\dot{V}_T/T_i$ as functions of simultaneously measured $PETCO_2$. Ventilatory responsiveness of each goat to CO_2 rebreathing was evaluated from slopes of these curves, from their intercepts on the $PETCO_2$ axis, and from values of $\dot{V}_E$ or $\dot{V}_T/T_i$ at $PETCO_2 = 70$ torr.

For statistical analysis, paired t-tests were performed to compare data obtained before and after adrenergic blockade. Data were tested for normality by the Wilk-Shapiro test (12). A p value <0.05 was considered statistically significant.

Results

The effects of beta blockade on the ventilatory responses to CO_2 rebreathing in each of the 5 goats are shown in Figure 2. There was no statistically significant difference in mean values of the slopes, the X-intercepts, or $\dot{V}_E$ at $PETCO_2 = 70$ for these lines before vs. after propranolol for the 5 goats (Table 1). We also assessed ventilatory drive by plotting $\dot{V}_T/T_i$ against $PETCO_2$ for the same CO_2 rebreathing tests. Again, there were no statistically significant differences in the mean slopes, the X-intercepts, or $\dot{V}_T/T_i$ calculated from the regression lines at $PETCO_2 = 70$ before vs. after propranolol (Table 1).

To assess the adequacy of propranolol infusion in blocking beta receptors, we compared heart rate responses to

isoproterenol infusion after the goats had received propranolol with heart rate responses to the same dose of isoproterenol in the absence of propranolol (Figure 3). The mean response of heart rate to isoproterenol was reduced by 86% after administration of propranolol. The mean ($\pm$ S.E.) baseline heart rate was somewhat lower after administration of propranolol (73 ± 10 to 63 ± 7 beats/min), but this difference was not statistically significant.

The ventilatory response to CO₂ rebreathing for each of the 5 goats before and after alpha-blockade with phentolamine is shown in Figure 4. There was no statistically significant change in mean values of the slopes, the X-intercepts, or $\dot{V}_E$ calculated at PETCO₂ = 70 after phentolamine administration (Table 2). When VT/Ti was plotted against PETCO₂, there was a slight but statistically significant decrease in slope and X-intercept after phentolamine administration. However, there was no difference in VT/Ti calculated from the regression line for PETCO₂ = 70 after (compared to before) phentolamine (Table 2).

To assess the adequacy of alpha-blockade, we compared the increase in arterial blood pressure in response to infusion of norepinephrine while the goat was receiving phentolamine with that seen in the absence of alpha blockade (Figure 5). Phentolamine did attenuate the pressor response to norepinephrine infusion by 76%, although there was no change in the average baseline mean blood pressure after phentolamine administration (83 ± 4 before vs. 82 ± 3 mm. Hg after phentolamine).

Discussion

In this study in goats, we found no significant effect of either alpha or beta adrenergic blockade on the response of minute ventilation or mean inspiratory flow to hyperoxic CO₂ rebreathing. That adrenergic receptors were adequately blocked is suggested by the minimal response to relatively large doses of the corresponding agonists.

There are several possible interpretations of our failure to see an effect of adrenergic blockade on CO₂ responsiveness in goats. First is the possibility that sympathoadrenal activity does not play a role in modulating CO₂ responsiveness. The fact that some investigators (9,13) have found effects of beta blockade on the ventilatory response to CO₂ suggests that the answer may be more complicated. Other potential effects of adrenergic blockers, such as alteration of CO₂ production or of physiologic deadspace, might secondarily affect resting ventilation or the measured response to ventilatory stimuli, and might differ among studies. On the basis of published data, it is difficult to determine whether discrepancies among studies can be explained in part by differences in these other effects.

Second is the possibility that the response to adrenergic blockers depends upon the level of baseline sympathoadrenal activity. Since there was no marked change in mean blood pressure after phentolamine or heart rate after propranolol, it is possible that baseline adrenergic tone was relatively low in these goats, accounting for our failure to see a change in CO₂ responsiveness after adrenergic blockade.

A third possibility is that adrenergic activity may

influence ventilation by altering the output of carotid chemoreceptors in normoxic conditions, but that this influence is suppressed in hyperoxic states (5, 16). Since our studies were all performed under hyperoxic conditions, carotid chemoreceptor activity was presumably suppressed, and might account for failure of manipulating adrenergic activity to influence the ventilatory response to CO₂ inhalation.

Whether adrenergic activity is altered as a result of the hypercapnia induced by CO₂ rebreathing cannot be answered without measurements reflecting sympathoadrenal activity, such as norepinephrine turnover or plasma catecholamine levels. However, even if such changes do occur, we do not think they influence ventilatory responsiveness to hyperoxic CO₂ rebreathing, which was not reduced following adrenergic blockade.

We conclude that, in our resting goats, neither basal adrenergic activity nor a change in adrenergic activity, if such occurred during hypercapnia, contributed to the ventilatory responses to CO₂ inhalation. Our findings suggest that if the sympathoadrenal system does influence ventilatory responses to CO₂ in mammals, then the goat may not be a good species in which to study this relationship. Additionally, if adrenergic activity influences ventilatory drive through the carotid body chemoreceptors, a normoxic or hypoxic test of ventilatory responsiveness might be required to demonstrate such an effect.

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In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," as prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council.

The views, opinions, and/or findings contained in this report are those of the authors and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other official documentation.

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TABLE 1
EFFECT OF BETA BLOCKADE ON CO₂ RESPONSE CURVES IN AWAKE GOATS

	MINUTE VENTILATION ($\dot{V}_E$)		$\dot{V}_E$ AT PETCO ₂ =70 TORR (L.min ⁻¹)
	SLOPE (L.min ⁻¹ .torr ⁻¹)	X-INTERCEPT (torr)	
CONTROL	1.77±0.35	54.3±2.0	25.9±3.1
PROPRANOLOL	1.55±0.29	54.1±2.1	23.0±3.4
P	NS	NS	NS
	MEAN INSPIRATORY FLOW (V_T/T_I)		V_T/T_I AT PETCO ₂ =70 TORR (L.min ⁻¹)
	SLOPE (L.min ⁻¹ .torr ⁻¹)	X-INTERCEPT (torr)	
CONTROL	3.84±0.84	52.7±2.0	60.6±7.2
PROPRANOLOL	3.48±0.72	53.1±2.1	54.0±7.2
P	NS	NS	NS

Values are means±SE; n=5.

TABLE 2
EFFECT OF ALPHA BLOCKADE ON CO₂ RESPONSE CURVES IN AWAKE GOATS

	MINUTE VENTILATION ($\dot{V}_E$)		
	SLOPE (L.min ⁻¹ .torr ⁻¹)	X-INTERCEPT (torr)	$\dot{V}_E$ AT PETCO ₂ =70 TORR (L.min ⁻¹)
CONTROL	1.95±0.40	53.2±2.6	29.6±3.8
PHENTOLAMINE	1.85±0.50	50.9±3.3	29.9±4.6
P	NS	NS	NS
	MEAN INSPIRATORY FLOW (V_T/T_i)		
	SLOPE (L.min ⁻¹ .torr ⁻¹)	X-INTERCEPT (torr)	V_T/T_i AT PETCO ₂ =70 TORR (L.min ⁻¹)
CONTROL	4.26±0.90	51.9±3.2	68.8±9.8
PHENTOLAMINE	3.78±1.02	48.0±3.9	70.1±11.1
P	<0.05	<0.05	NS

Values are means±SE; n=5.

FIGURES

FIG. 1 Representative example of breath-by-breath plot of triplicate CO_2 rebreathing studies on a single goat under a particular experimental condition. Breaths from each of the 3 studies are represented by a different symbol. The best-fitting straight line relating $\dot{V}_E$ to P_{ETCO_2} has been drawn.

FIG. 2 Effect of propranolol on CO_2 rebreathing. The lines relating $\dot{V}_E$ to P_{ETCO_2} before and after propranolol administration are shown for each of the 5 goats.

FIG. 3 Effect of propranolol on baseline heart rate ($\pm\text{SE}$) and the heart rate response to isoproterenol infusion.

FIG. 4 Effect of phentolamine on CO_2 rebreathing. The lines relating $\dot{V}_E$ to P_{ETCO_2} before and after phentolamine administration are shown for each of the 5 goats.

FIG. 5 Effect of phentolamine on baseline mean arterial blood pressure ($\pm\text{SE}$) and the blood pressure response to norepinephrine infusion.

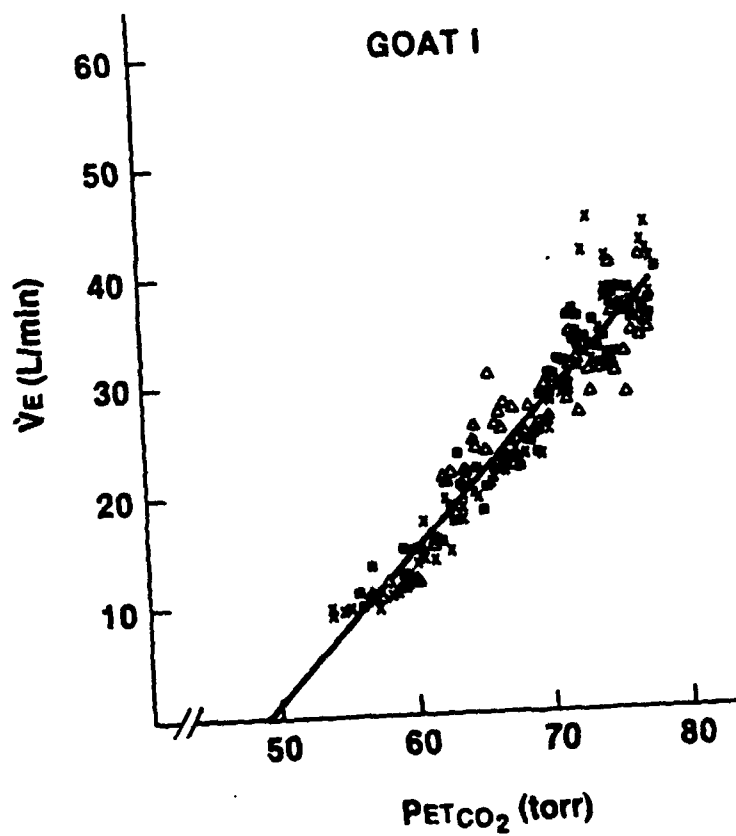


Figure 1

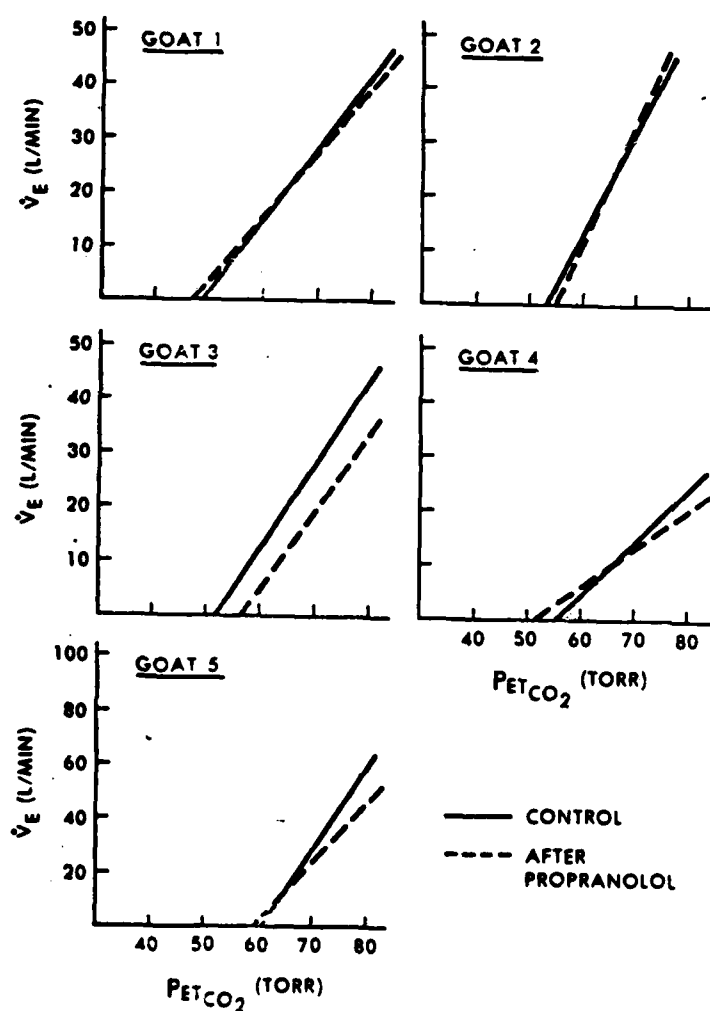


Figure 2

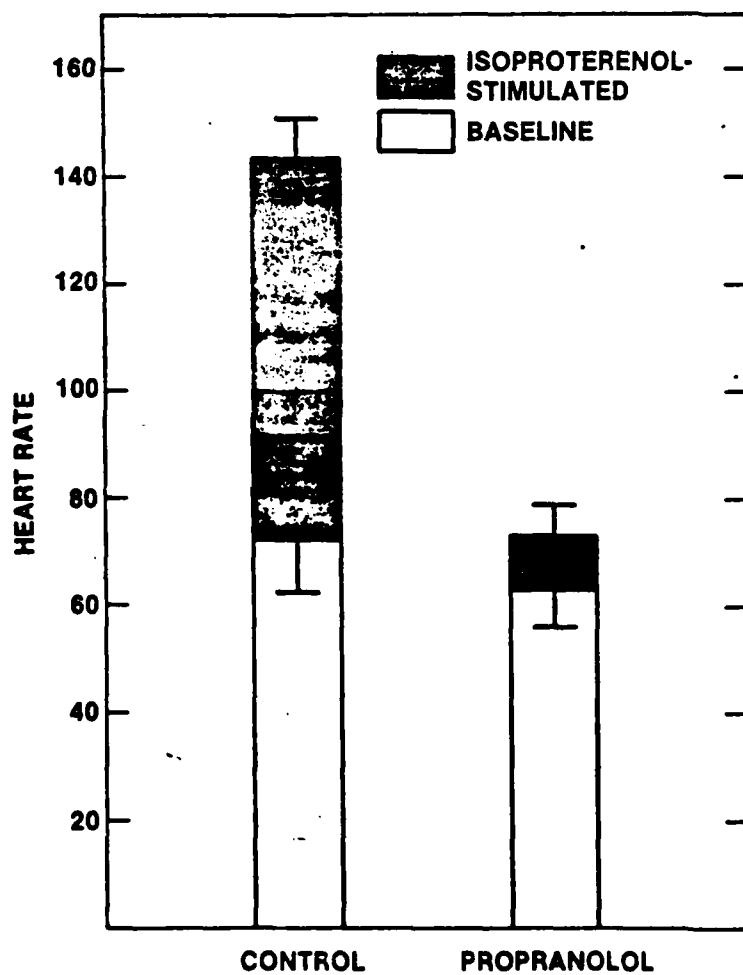


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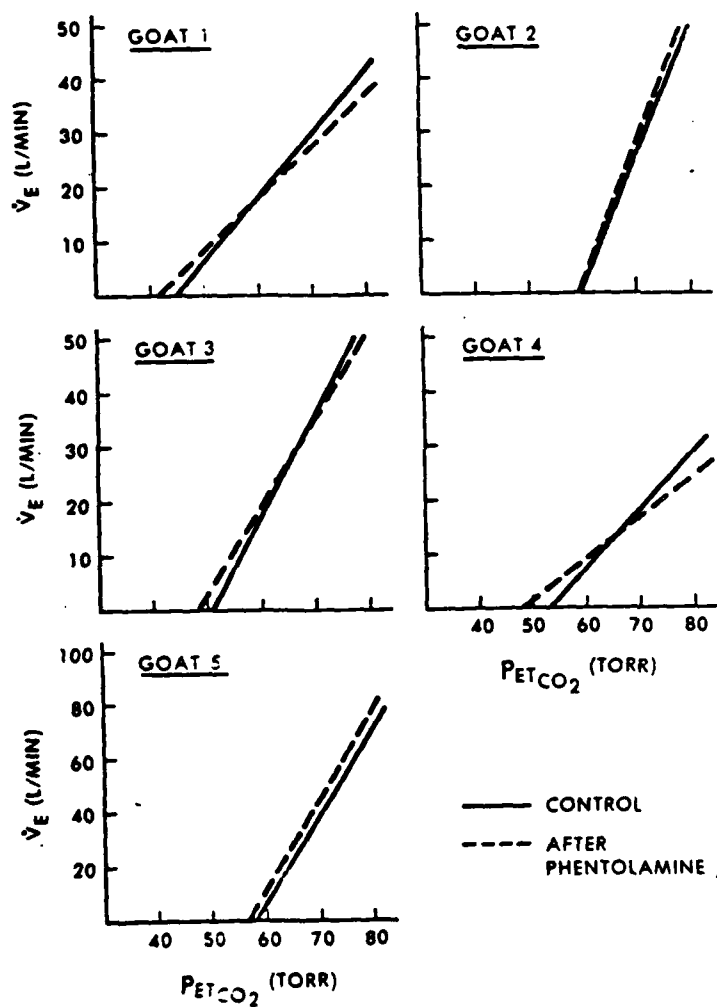


Figure 4

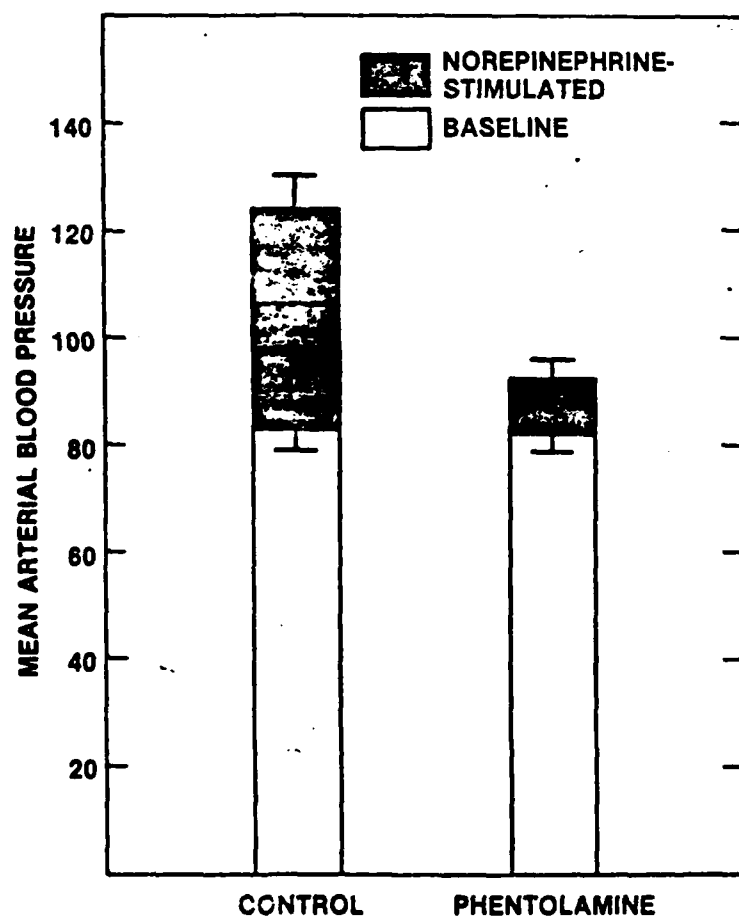


Figure 5

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