# Evidence for a Ventilation Modifying Reflex from the Pulmonary Circulation in Man.* (28687)

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Previous studies in anesthetized cats and dogs have demonstrated a lobeline sensitivity reflexogenic zone in the region of the pulmonary artery bifurcation(1). Stimulation of this area, which is known to contain pressoreceptors(2) causes reflex depression of ventilation, bradycardia and hypotension. The threshold for ventilatory change is lower than that for cardiovascular effect. As there is no evidence for this reflexogenic zone in man or unanesthetized animals, lobeline injections were made in conscious human volunteers in an attempt to demonstrate its presence.

Lobeline hydrochloride, in doses customarily used to determine circulation time (2.5-6.0 mg), was injected into the brachial vein of healthy, adult unanesthetized subjects. It caused depression of ventilation within the arm-lung circulation time, and in approximately half concomitant cardiovascular changes. Because of the short latent period between injection and response, these effects must be reflex in nature. By analogy with previous animal experimentation, these findings are considered strong evidence for the presence in man of a primarily ventilation modifying reflex originating from a reflexogenic zone in the wall of the extra pulmonary arteries.

*Methods.* Twenty healthy adults of either sex, age 20-45, most of whom were unaware of the changes anticipated, were volunteer subjects. All studies were made with the individuals supine; ventilatory velocity, measured with a pneumotachograph and lead II of the electrocardiogram were simultaneously recorded on a Sanborn Twin Viso. Tidal volume was obtained by planimetric or electronic integration of the velocity signal. Through a fast flowing saline infusion into the right antecubital vein, and at a time unknown to the subject, lobeline (30-40 $\mu$g/kg) was injected over a period of one second. The beginning of injection was marked on the record by an assistant. Five to 10 minutes after the initial dose of lobeline, twice as much was injected.

From this initial series of 20 studies, 4 lobeline-sensitive subjects who experienced no unpleasant sensory effects, nor strong desire to cough were selected for further investigation. Brachial artery pressure was measured with a transducer and recorded together with tidal volume on a Minneapolis-Honeywell-Visicorder. Lobeline in the dose previously shown to cause a response was given intravenously in the opposite arm. As before, the exact time of lobeline injection was marked on the trace.

Synthetic l-lobeline ($\alpha$-lobeline) hydrochloride 10 mg/ml (Sandoz) was used. A statistical level of significance is inferred when $P < 0.05$.

*Results.* In 17 of the 20 subjects, ventilatory depression was observed following lobeline injection (Fig. 1). Three showed no change. Typically, tidal volume and respiratory rate were reduced although sometimes the latter observation could not be made accurately as paroxysms of coughing and hyperventilation on occasions followed the first significantly depressed breath. Ventilation was considered depressed if the tidal volume was less than the smallest control tidal volume recorded continuously for 30 seconds to one minute prior to injection. When expressed as a percentage of mean control tidal volume, respiration was depressed 31.1 $\pm$ S.E. 3.8% ($n = 17$) range 10-70%. In 2 subjects (Fig. 1), a short period of apnea was observed. The mean latent period from the beginning of lobeline injection to the peak inspiratory velocity of the first depressed breath was 6.6 $\pm$ S.E. 0.5 second ($n = 17$) range 4-9 seconds.

A transient bradycardia was observed in 10 of the 17 subjects who showed ventilatory depression to lobeline (Fig. 1). A brady-

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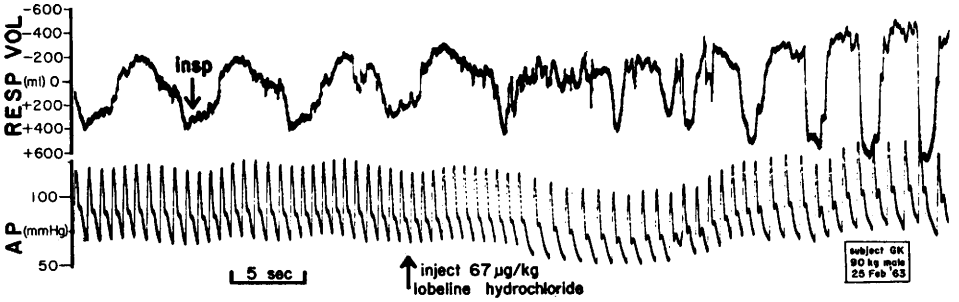


FIG. 1. Effect of intravenous injection of 6.0 mg lobeline hydrochloride on arterial pressure and respiratory volume of human subject. Ventilatory depression, bradycardia and hypotension occurred 7 to 8 sec. after administration.

cardia was considered significant when the R-R interval was greater than the longest control interval. The maximum slowing of the heart, when expressed as a percentage of mean control rate, was 28.0 ± S.E. 1.5% (n = 10) range 15-40%. Although there was no significant difference in the latent periods between injection and the ventilatory and cardiac reflex response, in several subjects the bradycardia followed the depression of tidal volume by one second. In 3 instances following injection of the larger dose of lobeline, the first slowed heart beat was associated with the brief inhibition of ventilation and increase of intrathoracic pressure that preceded a cough. To determine whether the bradycardia was caused by the increase in intrathoracic pressure, a vigorous Valsalva maneuver was carried out in these subjects to simulate this effect. On no occasion was a comparable bradycardia found. In these 3 cases the latent period from injection to depression of ventilation was measured following injection of the smaller dose of lobeline.

Analysis of the arterial pressure recordings (Fig. 1) showed that lobeline caused bradycardia, hypotension and a diminution in pulse pressure. The maximal slowing of heart rate was immediate, but the greatest hypotension and diminution of pulse pressure occurred 6-8 seconds after the beginning of bradycardia. Calculation of the approximate cardiac output from the product of pulse pressure and heart rate showed that a reduction followed lobeline injection in all instances. The total peripheral resistance calculated from these cardiac output values and the observed arterial pressure was reduced. This conclusion is reinforced by the observation that at the same arterial pressure, the slope of the diastolic pulse wave subsequent to the dicrotic notch is decreased during the peak hypotensive effect.

Utilizing the results from all subjects, the degree of ventilatory depression was compared in smokers and non-smokers. The mean respiratory depression for smokers was 31.4% and for non-smokers 18.1%; these figures are significantly different ($P < 0.03$). Of the 10 subjects who showed cardiovascular change, 7 were smokers. The mean ventilatory depression in those that showed no cardiovascular response was 23.7% in comparison to a mean change of 37.8%, which is significantly greater, in those with concomitant cardiovascular effects.

Symptoms varied a great deal in intensity, site and quality. Injection in some was asymptomatic while in others, it was moderately uncomfortable, although transient. Symptoms were most commonly localized to the mid-sternal region and the throat and larynx; they were described as burning, flushing, tickling, a sense of suffocation and irritation at both sites. A cough was noted almost always. Except in 3 instances (see above) coughing occurred after the bradycardia and depression of ventilation; this usually coincided with the beginning of hyperventilation which was 12-18 seconds after lobeline was administered. Many subjects volunteered that their symptoms occurred just before or at the same time that they consciously experienced the sensation of hyperpnea.

*Discussion.* Lobeline injected into the brachial vein causes depression of ventilation, bradycardia and hypotension within an average period of 6.6 seconds in unanesthetized man. These changes are the same as those found in anesthetized cats and dogs(1), and precede the well known responses of hypertension and hyperventilation due to chemoreceptor stimulation. Since cardiovascular changes are seen only with large and not with minimal degrees of ventilatory depression, it appears that the reflex threshold for ventilatory change is lower than that for the cardiovascular effects. Kinnison(3) has recently demonstrated in dogs that a fall of pressure in the pulmonary but not systemic circulations is associated with an increase in ventilatory rate and depth. Calculations suggest that hypotension results not only from the reduced cardiac output but also from a reduction in peripheral resistance. Animal experiments show that the reflex hypotension following lobeline is reduced but not eliminated by atropine(4). The latency of 6.6 seconds between injection and response lies within the arm-lung circulation time which has been shown to vary between 3 to 9.5 seconds(4,5,6), when the ether injection method is used, or 3 to 9.5 seconds when determined by paraldehyde injection(7). It is therefore reasonable to conclude that the early effects of lobeline occur before the blood has reached the cerebral, coronary or systemic circulations, and are most likely reflex changes elicited from between the site of injection and the pulmonary circulation. This conclusion is consistent with animal studies in which the site of lobeline reflexogenic action has been localized to the extra pulmonary arteries.

A similar triad of response in man has been reported by Page and McCubbin(8) following 1,1-dimethyl-4-phenylpiperazinium iodide (DMPP). This drug recently has been shown in cats to cause the same reflexogenic changes as lobeline(9). Plavsic(10), who employed lobeline for circulation time studies, described a period of apnea in some patients which preceded hyperventilation.

The depression of ventilation occurred before the cough or other symptoms which might cause a change in the breathing pattern. Bradycardia was not due to the increased intrathoracic pressure that preceded coughing nor was it caused by an arterial pressure change and baroreceptor response. Eckenhoff and Comroe(11) demonstrated that the lobeline-induced symptoms are blocked by tetraethylammonium chloride and suggested that they originated from pleural or bronchial pain sites. All reflex cardiorespiratory changes to lobeline are also blocked by this drug in doses smaller than those that block the autonomic ganglia(4) presumably by an action at the sensory ending itself. It is unknown whether stimulation of the same sensory ending is responsible for the cardio-respiratory effects and the visceral sensations, although the different latencies suggest that this is unlikely. The increased response to lobeline seen in smokers probably reflects an additive action of lobeline with its pharmacological analogue nicotine although other explanations are possible. Nicotine has similar actions to lobeline on the pulmonary artery reflexogenic zone. (Bevan, unpublished results).

These experimental findings in man demonstrate the presence of a primarily ventilation regulating reflexogenic area between site of injection and pulmonary circulation. Previous definite animal studies, also with lobeline, suggest that this is a pressoreceptor area in the region of the bifurcation of the pulmonary artery. Cardiovascular changes of bradycardia and hypotension are associated with this ventilatory change.

*Summary.* Lobeline injected intravenously into normal human subjects caused ventilatory depression in most and concomitant bradycardia and hypotension in a smaller number. These effects occurred within the arm-lung circulation time. These findings are considered strong evidence for a ventilation regulating reflexogenic area between the large veins and the pulmonary circulation in man. As demonstrated by previous animal experiments, the response probably originates from a pressure sensitive reflexogenic area in the region of the bifurcation of the pulmonary artery.

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## Effect of Tranquilizers on Libido, Sperm Production and *in vitro* Sperm Survival in Dogs.* (28688)

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Tranquilizing drugs, such as chlorpromazine (Thorazine) and promazine (Sparine), have been shown by many workers to inhibit ovulation by interfering with the release of luteinizing hormone (LH). However, Purshottam *et al*(1) have reported that chlorpromazine and promazine inhibit ovulation in mice on a PMS-HCG regimen normally resulting in superovulation; thus, an exogenous source of LH failed to induce ovulation. Barraclough and Sawyer(2) also have demonstrated that chlorpromazine may block the hypothalamic inhibition of luteotropin secretion. Information on the effect of tranquilizers on reproductive function in the male is negligible. Interference with the normal secretion of pituitary gonadotropins in males could occur, but the lack of "ovulatory peaks" may diminish observable effects on gonadotropin inhibition in the male. Gillette (3) and Zimbardo and Barry(4) found that the copulation rate, but not the percentage of rats which would copulate, was reduced by chlorpromazine administration. Direct cellular effects of chlorpromazine and promazine also are known to occur. *In vitro* studies by Foote and Gray(5) indicated that the motility and fertility of bull sperm were unaffected by 200 μg/ml of chlorpromazine, but higher levels of chlorpromazine and promazine were spermicidal. This report is a study of the effect of chlorpromazine and promazine on reproductive function in male dogs.

*Materials and methods.* Nine mature Beagle dogs weighing from 9 to 11 kg were used. The dogs had been trained for routine semen collection as described by Boucher *et al*(6). Semen samples were collected every third day. The procedure for evaluating, processing and storing the semen in a yolk-citrate-glucose-glycine-antibiotic medium has been described(5,7). The levels of promazine and chlorpromazine tested in the *in vitro* experiments corresponded to levels tested by Foote and Gray(5) with bull sperm. These experiments were completed prior to the time the dogs were administered tranquilizer.

Chlorpromazine was administered orally at the rate of 4.4 mg/kg (2 mg/lb), a dose slightly above the recommended dose given by Scheidy and McNally(8) for sedation. For this phase of the work dogs were paired on the basis of equal sperm output per ejaculate. One member of each of the 4 pairs was randomly assigned to Group A, and the other member to Group B. During period I all dogs were given 5 doses of chlorpromazine

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