

# Reflex Cardiovascular Depression Produced by Stimulation of Pulmonary Stretch Receptors in the Dog

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**ABSTRACT** To study the possible reflex effects of stimulation of pulmonary stretch receptors on the cardiovascular system, experiments were designed that would allow separate assessment of the responses of the heart, the total peripheral vascular resistance, and the resistance of the innervated hindlimb that was perfused at a constant flow rate. In every experiment, inflation of the lungs to a positive pressure of 20 mm Hg produced significant negative inotropic and chronotropic effects. Heart rate fell an average of  $22.3 \pm 3.8\%$  (SEM) ( $P < 0.01$ ), pressure recorded from within an isovolumic balloon in animals on total cardiopulmonary bypass fell an average of  $14.3 \pm 4.6\%$  ( $P < 0.05$ ), dp/dt recorded from within the balloon declined an average of  $31.4 \pm 6.0\%$  ( $P < 0.01$ ), and contractile force measured with a Walton-Brodie strain gauge arch fell an average of  $18.6 \pm 2.2\%$  ( $P < 0.01$ ). Similarly, a depressor response to inflation of the lungs was noted in the periphery as manifested by an average decrease in total peripheral vascular resistance of  $21.9 \pm 2.5\%$  in the animals on total cardiopulmonary bypass ( $P < 0.01$ ), and by an average decrease in perfusion pressure in the isolated hindlimb of  $26.0 \pm 3.8\%$  ( $P < 0.01$ ). After bilateral cervical vagotomy, the cardiovascular responses to inflation of the lungs were either abolished or markedly lessened. Thus, sudden expansion of the lungs activates the afferent arm of a depressor reflex, which produces negative inotropic and chronotropic

responses, in addition to arterial vasodilation. The receptors are sensitive to stretch and the afferent pathway runs predominantly in the vagus nerves.

## INTRODUCTION

One of the best known and firmly established of all reflexes is the Hering-Breuer reflex, which refers to the inhibition of the respiratory center produced by stimulation of pulmonary stretch receptors. However, the question of whether these pulmonary stretch receptors also influence the cardiovascular system remains unsettled. Using electroneurographic techniques, Adrian, Bronk, and Phillips (1), and Joels and Samueloff (2) reached the conclusion that increases in nerve traffic in sympathetic nerves are synchronous with the increase in nervous activity recorded from the phrenic nerve during inspiration. That is, inspiration is associated with augmented sympathetic activity. Exactly opposite conclusions were reached by Bronk, Ferguson, Margaria, and Solandt (3), Downing and Siegel (4), and Okada and Fox (5), all of whom found that, when respiratory groupings were present, inspiration was generally associated with a decrease in sympathetic nervous activity. This latter view has been supported by Salisbury, Galletti, Lewin, and Rieben (6) and by Daly, Hazzledine, and Ungar (7), who noted that systemic arterial pressure fell when the lungs were expanded. The interpretation of the data that has been accumulated by these investigators has been complicated by the fact that in some of the studies the experimental animals breathed spontaneously (1, 5), in some they were artificially ventilated (3-7), and in some studies gas exchange was produced by diffusion respiration (2). To try to resolve the question of whether or not pul-

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monary stretch receptors exert control over the cardiovascular system, experiments were designed that would allow separate assessment of the possible reflex effects of positive pressure inflation of the lungs on cardiac function and on the resistance of an isolated vascular bed, together with a reinvestigation of the effects produced by inflation of the lungs on the total peripheral vascular resistance.

## METHODS

*Reflex effects on the heart.* To investigate the possible role of the pulmonary stretch receptors in the control of cardiac performance, we performed experiments on 13 dogs that were placed on total cardiopulmonary bypass, on four dogs that were placed on right heart bypass and on two closed-chest dogs. These animals, weighing between 17.0 and 27.2 kg, were anesthetized with a combination of morphine sulfate (3 mg/kg subcutaneously), urethane (480–960 mg/kg intravenously) and alpha-chloralose (48–96 mg/kg intravenously). Sudden inflation of the lungs was produced by positive pressure obtained either from a Bennett respirator or from a pressure bottle that was attached to a cuffed endotracheal tube by a side arm. Between interventions the lungs were ventilated by means of a respirator (Harvard Apparatus Co., Inc., Dover, Mass.) at a normal rate and with a tidal volume varying between 400 and 700 ml; the sudden lung inflations were initiated from the end-expiratory position. The actual pressures within the trachea were not recorded. Room air was used to ventilate the lungs in 10 dogs and 100% O<sub>2</sub> was used in three dogs.

In the 13 experiments utilizing total cardiopulmonary bypass, drains were placed in the inferior and superior vena cavae and in the right ventricle to collect the entire systemic venous return. This blood was then pumped at a constant rate by a roller pump through a disc oxygenator where it was exposed to a gas mixture containing 97% O<sub>2</sub> and 3% CO<sub>2</sub>, and then through a heat exchanger back into the systemic circulation via the subclavian artery. A vent was placed in the left ventricle via the left atrium to drain blood returning to this chamber from the bronchial and Thebesian circulations. The pulmonary artery was tied off in four dogs to prevent possible activation of baroreceptors that are known to be present in this vessel (8).

The effects of inflation of the lungs on the myocardial contractile state were determined in two ways. First, in eight of these animals isometric contractile force was measured by means of a Walton-Brodie strain gauge arch that was sutured to the left ventricle in six dogs and to the right ventricle in two; contractile force was not calibrated in absolute terms but was assessed in millimeter deflection. Second, in seven of these animals on total cardiopulmonary bypass, a small balloon containing 1–4 ml of saline was attached to a wide bore metal cannula and was passed via the left atrial appendage through the mitral valve into the left ventricle. Changes in absolute pressure developed within the balloon and in the maximal rate of pressure rise, dp/dt, were taken as indices of changes in myocardial contractile state. Pressures were constantly monitored from the femoral artery and the right atrium, and from the pulmonary artery in those experiments in which it was not tied off. The effect of inflation of the lungs on heart rate was determined in 10 of these dogs; in the other three, cardiac arrhythmias precluded evaluation. To avoid possible artefacts resulting from changes induced concomitantly in ar-

terial pressure, we maintained aortic pressure constant in five studies by rapidly infusing blood from a pressure bottle via a large bore cannula inserted into the femoral artery.

In the four dogs studied while on right heart bypass, large catheters were placed in the inferior and superior vena cavae and in the right ventricle to collect the entire systemic venous return. In two of these animals it was then pumped by means of a roller pump, through a heat exchanger, directly into the pulmonary artery. In the other two animals, a disc oxygenator was interposed in the circuit and the blood was fully oxygenated before it was returned to the pulmonary artery. Isometric myocardial contractile force was measured in two of these dogs by means of a Walton-Brodie strain gauge arch sutured to the surface of the left ventricle, and in the other two a wide bore metal cannula was inserted into the left ventricle (LV) through the apical dimple and the maximum rate of pressure rise, LV dp/dt, was determined. Heart rate was measured in all four animals.

In the two closed-chest dogs, heart rate was measured before and after inflation of the lungs. Right ventricular dp/dt was determined in one of these dogs by means of a catheter tip micromanometer (model SF-1, Statham Instruments, Inc., Los Angeles, Calif.) passed via the external jugular vein into the right ventricle, and in the other, left ventricular dp/dt was measured by means of a similar micromanometer passed retrograde through the aortic valve.

*Reflex effects on the resistance vessels.* Peripheral vascular resistance was studied in two different experimental models. In the first preparation, aortic pressure was constantly monitored in the 13 dogs placed on total cardiopulmonary bypass as described above. Since in any given experiment the output of the pump was held constant, changes in trunk pressure reflected alterations in total peripheral vascular resistance. In the second preparation, described in detail previously (9), the normally innervated, isolated hindlimb was perfused at a constant flow rate in 13 experiments so that changes in perfusion pressure directly reflected changes in vascular resistance in the hindlimb. Of the 13 perfused hindlimb preparations, five were performed in dogs on total cardiopulmonary bypass, four in dogs on right heart bypass, and four in dogs with intact chests.

*Vagotomy.* In 14 studies, experiments were performed before and after bilateral cervical vagotomy.

## RESULTS

*Effects of inflation of the lungs on the heart.* In every experiment, inflation of the lungs to a positive pressure of 20 mm Hg produced significant negative inotropic and chronotropic effects as illustrated by a representative study shown in Fig. 1 and by the results from the entire group of dogs graphed in Fig. 2. The data in Fig. 2 represent the maximum changes produced in the variables by inflation of the lungs. Heart rate fell significantly ( $P < 0.01$ ), declining by an average of  $22.3 \pm 3.8\%$  (SEM), from a mean control value of  $172.1 \pm 5.8$  to  $136.4 \pm 8.9$  beats/min (Fig. 2 C). Similarly, the absolute pressure within the balloon inserted into the left ventricle in animals on total cardiopulmonary bypass fell by an average of  $14.3 \pm 4.6\%$  ( $P < 0.05$ ), from a control level of  $118.8 \pm 15.8$  mm Hg to  $98.6 \pm 15.9$  mm Hg (Fig. 2 A). The maximum rate of pressure rise re-

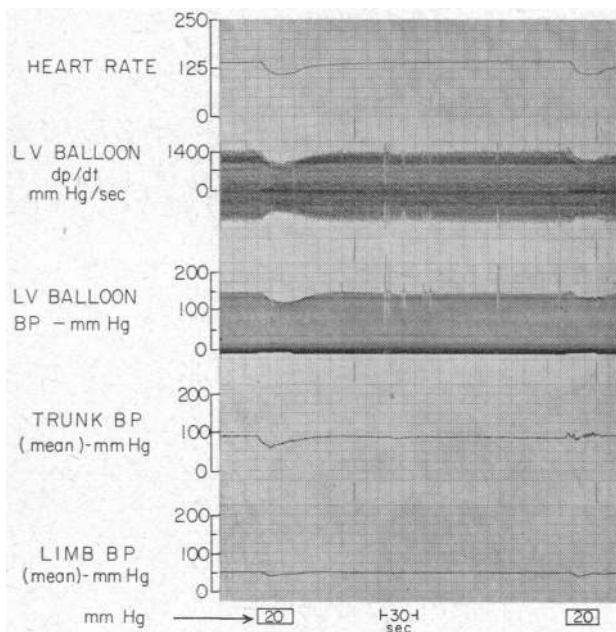


FIGURE 1 Effects of inflation of the lungs in a dog on total cardiopulmonary bypass. The horizontal bar indicates inflation to a positive pressure of 20 mm Hg. On the left, heart rate, dp/dt of an isovolumic balloon in the left ventricle, the absolute pressure developed within the balloon, and trunk and perfused hindlimb pressure all decrease during inflation. On the right, trunk pressure is kept relatively constant during inflation of the lung, but heart rate, dp/dt, and perfusion pressure in the hindlimb still decrease. LV = left ventricle.

corded from within the balloon declined by an average of  $31.4 \pm 6.0\%$  ( $P < 0.01$ ), from a control value of  $1478 \pm 173$  mm Hg/sec to  $1025 \pm 155$  mm Hg/sec (Fig. 2 B). Ligation of the pulmonary artery produced no significant differences in these depressor responses. In the two animals on right heart bypass, left ventricular dp/dt fell 52 and 33%; in the two dogs with intact chests, right ventricular dp/dt fell 18% in one and left ventricular dp/dt decreased 40% in the other. Isometric contractile force declined by an average of  $18.6 \pm 2.2\%$  ( $P < 0.01$ ), from a control value of  $28.7 \pm 0.9$  mm deflection to  $23.4 \pm 1.1$  mm deflection (Fig. 2 D).

As shown in Fig. 1, the negative inotropic and chronotropic effects produced by sudden inflation of the lungs occurred even though aortic pressure was maintained at a relatively constant level by rapidly infusing blood from a buffer bottle inserted into the femoral artery. The results obtained from dogs whose lungs were ventilated with room air were qualitatively the same as those obtained from animals whose lungs were ventilated with 100% O<sub>2</sub>. In most of the animals the depression of myocardial performance produced by inflation of the lungs was related to the magnitude of the stimulus, the thresh-

old occurring at about 10 mm Hg. However, in a few animals, no cardiovascular response was noted until the distending pressure of the lungs had reached 20 mm Hg. When the lungs were deflated, the variables returned to control levels in a matter of seconds. Moreover, if pulmonary distention was maintained, the variables would usually start to return to control values in 15–25 sec (Figs. 1, 3, and 5).

*Effects of inflation of the lungs on peripheral vascular resistance.* In every experiment, vascular resistance fell

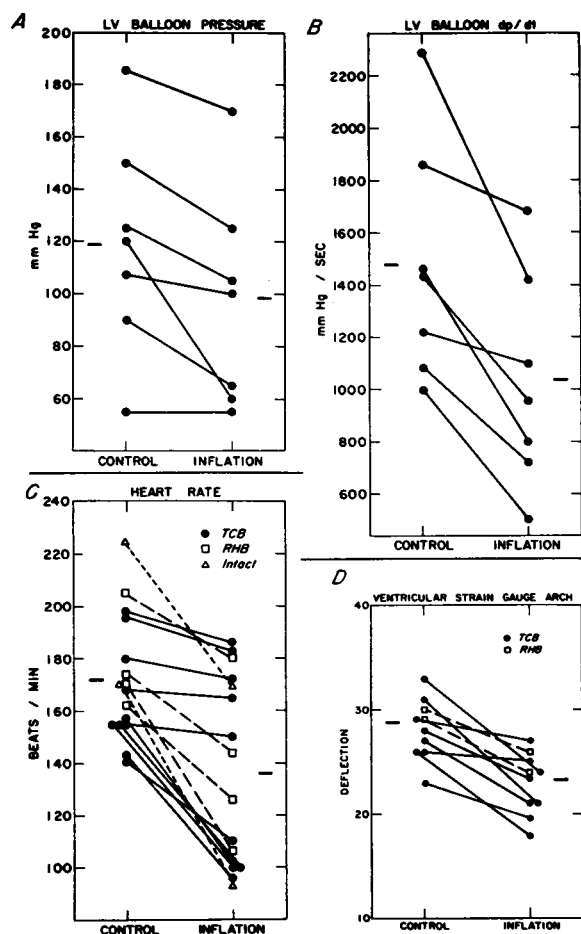


FIGURE 2 Effects on the heart of inflation of the lungs to a pressure of 20 mm Hg. A) Effects on peak absolute pressure recorded from within an isovolumic balloon inserted into the left ventricle of dogs on total cardiopulmonary bypass. B) Effects on the maximum rate of pressure rise as recorded from the isovolumic balloon. C) Effects on heart rate. D) Effects on isometric contractile force as recorded by a Walton-Brodie strain gauge arch. TCB = total cardiopulmonary bypass. RHB = right heart bypass. Intact = closed-chest dog. The horizontal lines on each side of the individual panels represent the average values for all the dogs during the control period and during inflation of the lung.

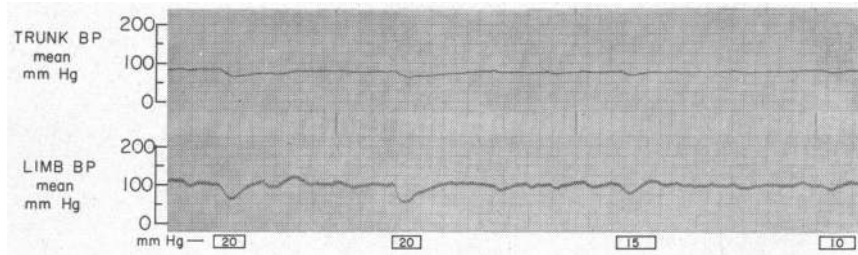


FIGURE 3 The effects of inflation of the lungs to various positive pressures on the mean pressures recorded from the trunk and from the perfused hindlimb in a dog on total cardiopulmonary bypass. The reflex response is related to the magnitude of the stimulus. Paper speed = 0.25 mm/sec.

as a result of inflation of the lungs whether it was assessed by measuring arterial pressure in dogs on total cardiopulmonary bypass or by measuring perfusion pressure in the isolated perfused hindlimb preparation (Figs. 4 and 5), and the response was generally related to the magnitude of the stimulus (Fig. 3). Bronk et al. and Daly and his co-workers also found that the degree of sympathetic depression was related to the extent of pulmonary inflation (3, 7). As illustrated in Fig. 4, left, when the lungs of dogs placed on cardiopulmonary bypass were expanded to a positive pressure of approximately 20 mm Hg, trunk pressure and, there-

fore, total peripheral vascular resistance fell by an average of  $21.9 \pm 2.5\%$  ( $P < 0.01$ ), the trunk pressure declining from an average control level of  $81.5 \pm 4.9$  mm Hg to  $64.1 \pm 5.0$  mm Hg. The right panel of Fig. 4 demonstrates that the perfusion pressure in the isolated hindlimb also fell in each study, the decline averaging  $26.0 \pm 3.8\%$  ( $P < 0.01$ ), falling from a control level of  $77.6 \pm 7.5$  mm Hg to  $55.8 \pm 4.8$  mm Hg. As noted with the cardiac depression, the vasodepressor component of the reflex appears to be a rapidly adapting one.

*Effects of vagotomy.* Bilateral cervical vagotomy was performed in the course of 14 experiments. The

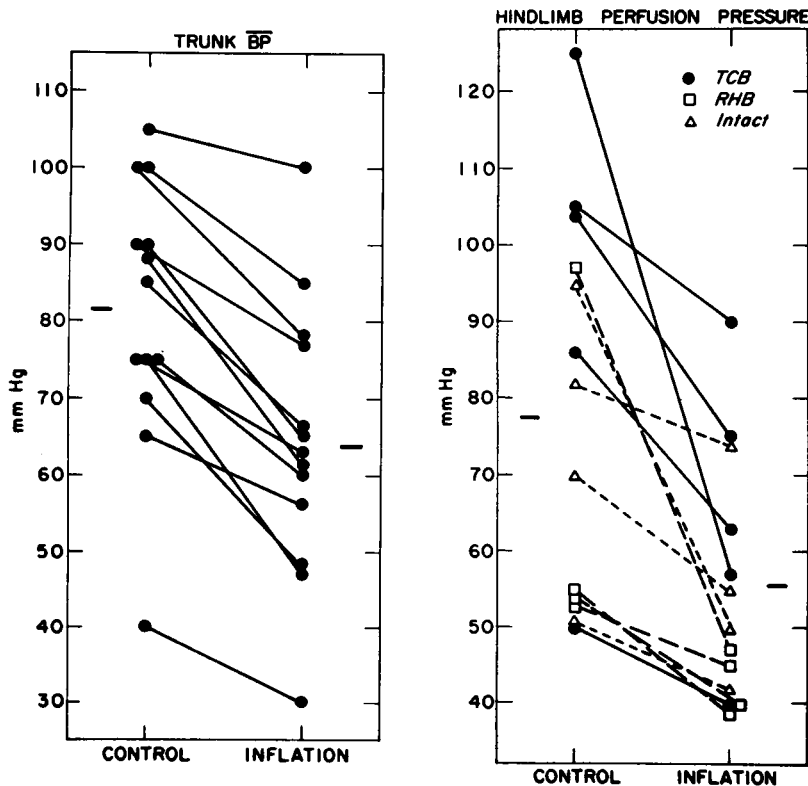


FIGURE 4 Left: Effect of inflation of the lungs to 20 mm Hg on mean arterial pressure recorded from the trunk in dogs on total cardiopulmonary bypass. Right: Effect of inflation of the lungs on the mean perfusion pressure recorded from the isolated hindlimb preparation. TCB = total cardiopulmonary bypass. RHB = right heart bypass. Intact = closed-chest dog. The horizontal lines at the side of each panel represent the average values for all the dogs during the control period and during inflation of the lungs.

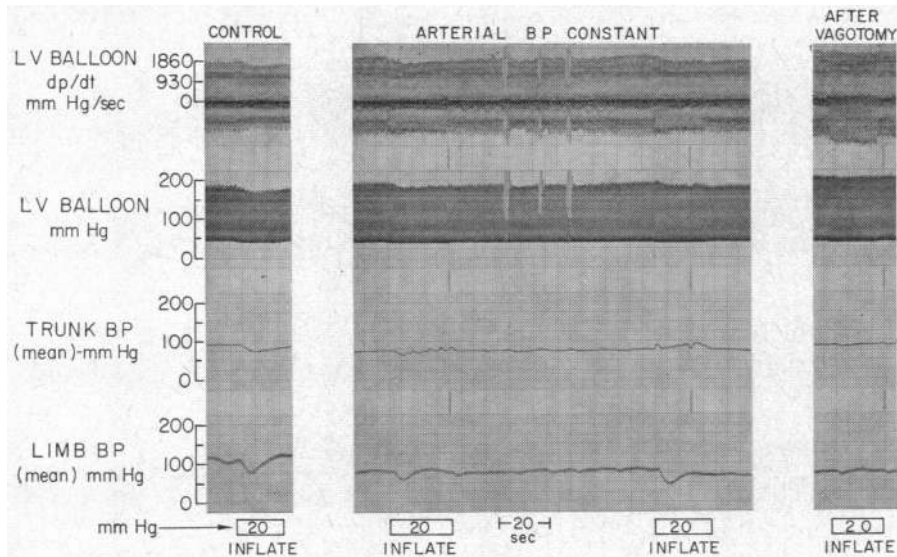


FIGURE 5 Effects of inflation of the lungs to 20 mm Hg on balloon  $dp/dt$ , on the absolute level of pressure recorded from the balloon, and on the trunk and hindlimb perfusion pressures. The left panel shows the decrease in  $dp/dt$  and in trunk and perfusion pressures when the lungs are distended. The center panel shows that the decreases in  $dp/dt$  and in hindlimb pressure occur even when arterial pressure in the trunk is kept constant. The right panel shows that after bilateral cervical vagotomy, the reflex is markedly diminished. LV = left ventricle.

tracing from a typical experiment is illustrated in Fig. 5, and it shows that the effects on the cardiovascular system produced by inflation of the lungs were markedly lessened by interruption of the vagus nerves.

## DISCUSSION

Partly in confirmation of previous findings (6, 7) the results of the present investigation clearly indicate that pulmonary stretch receptors do affect cardiovascular function, and that their activation results in reflex inhibition of sympathetic tone with consequent decreases in myocardial performance, heart rate, and peripheral vascular resistance. That these observed depressor responses are indeed reflex in nature rather than the result of mechanical effects produced by inflation of the lungs is indicated by the fact that they were observed in animals on right heart bypass, which means that they were not merely the result of induced changes in venous return, since blood flow into the pulmonary artery was kept constant. In addition, since the depressor responses were also present in the empty, nonejecting hearts of dogs placed on total cardiopulmonary bypass, they could not be the result of alterations in preload or afterload. Since ligation of the pulmonary artery did not influence the reflex depression that was produced, stimulation of pulmonary arterial baroreceptors is probably not important for the initiation of the reflex. Finally, the

decrease in myocardial contractile state that was observed could not simply be the result of diminished coronary blood flow consequent to the fall in aortic pressure, because reflex cardiac depression persisted even when aortic pressure was maintained constant. The fact that reflex cardiac depression occurred when the lungs were inflated despite a fall in systemic arterial pressure, a hemodynamic event that is normally associated with increased sympathetic discharge to the heart, suggests that the cardiac depressor response initiated by stimulation of pulmonary stretch receptors is capable of overcoming reflexes originating from the carotid sinus and aortic arch baroreceptors.

In addition to overcoming the antagonistic effects of the baroreceptor reflex in relation to the heart, the pulmonary stretch reflex is also capable of overriding its influence on the systemic arterial bed. Thus, reflex vasodilation occurs in the isolated perfused hindlimb as a result of inflation of the lungs at a time when pressure in the trunk is falling (Figs. 1 and 5), a circumstance that is ordinarily associated with an increase in vascular resistance of the hindlimb mediated by the arterial baroreceptor mechanism (10). Our observation that decreases in total peripheral vascular resistance occur during inflation of the lungs in dogs placed on total cardiopulmonary bypass confirms the findings of Salisbury and associates (6) and of Daly and coworkers (7).

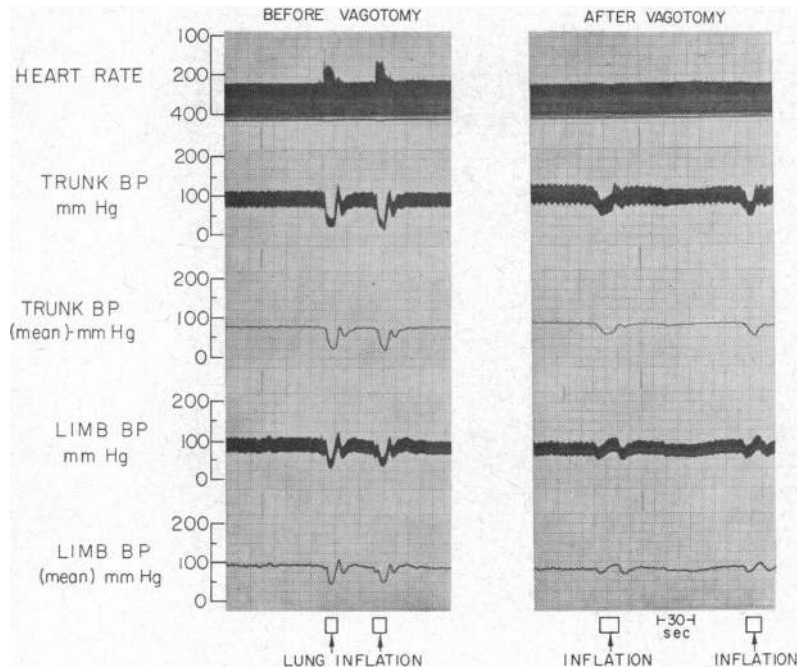


FIGURE 6 The effects of inflation of the lungs in a closed chest dog. Before vagotomy (left panel), heart rate decreases, and trunk and hindlimb perfusion pressures fall. After vagotomy (right panel), inflation of the lungs no longer has any effect on heart rate. The fall in arterial pressure in the trunk is lessened and results probably from a reduction in venous return, and hindlimb perfusion pressure rises slightly as a result of the arterial baroreceptor reflex.

The cardiovascular depressor reflex initiated by positive pressure inflation of the lungs is relatively rapidly adapting, a detectable fall occurring within 3–5 sec with a return toward control values usually beginning between 15 and 25 sec (Figs. 1, 3, and 5). In most experiments the variables attained control levels despite continued inflation of the lungs, but in some studies a slight depression remained throughout the lung inflation.

Since bilateral cervical vagotomy either abolishes or markedly lessens the cardiac and vasomotor effects of inflation of the lungs, the majority of the afferent fibers that mediate the stretch reflex must travel in the vagus nerves. This conclusion is consonant with the observations of Salisbury et al. (6) and Daly et al. (7) who studied the effects of the pulmonary stretch reflex on the total systemic vascular bed. The marked diminution in the depressor effects after vagotomy further supports the contention that they are the result of a reflex rather than the consequence of mechanical changes produced in the circulation as a result of inflation of the lungs.

The apparent disparity in the literature regarding the effects of inspiration on sympathetic nervous activity probably stems from several facts. Those investigators who used dogs with intact chests noted that significant changes in arterial pressure occurred as a result of changes in the intrathoracic pressure produced by respiration (1, 5). Thus, the baroreceptors were undoubtedly stimulated by the intervention and the sym-

thetic nervous activity that was measured was probably the resultant effect of the balance between the baroreceptor reflex and the pulmonary stretch reflex. That such a balance does indeed exist is substantiated by the findings of Daly and coworkers who observed that the magnitude of vasodepression produced by inflation of the lungs was related to the pressures within the baroreceptor areas located within the carotid sinus and aortic arch regions (7). In the study reported here, since open-chest dogs were used in all except two experiments, changes in arterial pressure resulting from changes in intrathoracic pressure were avoided. The concomitant influence exerted by the baroreceptors and by the pulmonary stretch receptors could also account for the differences observed after vagotomy in the present study compared to the findings of Adrian, et al. (1) and Okada and Fox (5). These investigators noted that vagotomy either had no effect or actually produced grouping of sympathetic impulses during expansion of the lungs. However, in their studies spontaneous inspiration was associated with a fall in arterial pressure which would lead to enhanced sympathetic activity, especially after the counterbalancing effect of the pulmonary stretch reflex had been removed by vagotomy. Joels and Samueloff correlated sympathetic traffic with respiratory center activity manifested by nerve impulses in the phrenic or recurrent laryngeal nerve, but did not actually expand the lungs (2). These workers came to the conclusion that inspiration is associated with increased sympathetic activity. However, those investiga-

tors who measured sympathetic impulse traffic during expansion of the lung found a decrease in sympathetic activity (3-5), which is consistent with our physiologic observations.

Since the depressor effects of the stretch reflex are also observed in closed-chest animals, this reflex may be of clinical importance. Its possible clinical significance becomes apparent when the settings in which positive pressure ventilation is used are considered. Thus, patients in acute pulmonary edema, in acute asthmatic attacks, with chronic lung disease, in the immediate postoperative period, and under general anesthesia in the operating room are endangered not only by the decrease in venous return that is known to result from positive pressure respiration, but also by a potentially powerful cardiovascular depressor reflex triggered by activation of pulmonary stretch receptors. These combined effects are illustrated in Fig. 6. On the left, a decrease in heart rate and marked falls in trunk pressure and in hindlimb perfusion pressure are produced by suddenly expanding the lungs in a closed-chest dog. After vagotomy, as shown on the right, the bradycardia no longer occurs, the fall in trunk pressure is much smaller and is probably the result of decreased venous return, and the fall in hindlimb perfusion pressure is converted to a rise presumably as a result of the arterial baroreceptor reflex.

In summary, sudden inflation of the lungs activates the afferent arm of a depressor reflex, which produces negative inotropic and chronotropic responses, coupled with arterial vasodilation. The receptors are sensitive to stretch and the afferent pathway runs predominantly in the vagus nerves.

## ACKNOWLEDGMENT

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