The Lungs as Receptor Sites for Cardiovascular Regulation

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SUMMARY The heart and lungs contain numerous receptors that, when activated, can modulate the behavior of the heart and blood vessels. However, the separate roles of these two organs in causing the reflex circulatory adjustments are difficult to assess. Present evidence indicates that the lungs can tonically inhibit the vasomotor center and that lung inflation causes a reflex decrease in blood pressure as a result of dilatation of systemic vessels, bradycardia and a negative inotropic effect on the ventricles. This lung inflation-vasodepressor reflex is due to activation of low-threshold pulmonary stretch receptors, subserved by vagal afferents. The inhibition exerted by the lungs on the limb and kidney vessels is similar during normocapnia but, in certain species, the inhibition of the renal vessels becomes much greater during hypercapnia. Thus, receptors in the lungs may preserve renal blood flow during respiratory acidosis and therefore contribute to the restoration of acid-base balance. The lung inflation reflex also modulates the response to activation of the arterial chemoreceptors by attenuating the chemoreceptor-induced bradycardia and peripheral vasoconstriction. During diving, the annulment of the pulmonary depressor reflex by the reflex respiratory arrest permits the full expression of the trigeminal reflex and chemoreflex so that the arterial blood pressure is maintained by constriction of systemic vessels and the available oxygen is distributed to the most vulnerable systems, the brain and lungs.

Other lung receptors can also affect the cardiovascular system in abnormal circumstances. Juxtapulmonary capillary receptors linked to nonmedullated vagal afferents can be activated by pulmonary congestion to cause reflex bradycardia, tachypnea and depression of the somatic nervous system. Mechanoreceptors in the pulmonary arteries, when activated with pressure up to 60 mm Hg, cause systemic hypotension and occasional bradycardia; with higher pressures, the systemic pressure increases. Some mechanoreceptors in the lung parenchyma, which increase their discharge with lung inflation, are subserved by medullated fibers that pass in the sympathetic nerves to the spinal cord. Their function is unknown.

IN THE PAST 25 YEARS, our knowledge of the lung has advanced remarkably. Much is now known of its ultrastructure, gas mixing, distribution and exchange, the control of the breathing patterns, the effects of gravity on the pulmonary circulation, the measurement and distribution of lung water, hypoxic constriction of the pulmonary vessels, surfactant from the alveolar type II cells, and the ability of the endothelial cells of the lung capillaries to remove, produce or modify bioactive materials.2 Attention has also been focused on the receptors in the tracheobronchial tree and lung parenchyma. While their precise morphology, distribution and function have yet to be established, observations indicate that four types are present: pulmonary stretch receptors, cough receptors, irritant receptors and juxtapulmonary capillary receptors.3,4 Since Hering and Breuer5 reported that distention of the lungs of anesthetized animals decreases the frequency of inspiratory efforts, whereas collapse has the opposite effect, the classic Hering-Breuer inflation reflex, it is generally accepted that the primary role of lung receptors is the modulation of the pattern of breathing. The activation of at least some of these receptors also causes reflex changes in the cardiovascular system. In this report the evidence for this is reviewed briefly, and the question is raised as to whether such changes are the results of abnormal circumstances induced by the laboratory procedures or whether such reflexes have a role in normal circumstances.

History

In 1867, von Bezold and Hirt6 noted that veratrum alkaloids injected intravenously into anesthetized rab-
bits caused a decrease in heart rate and blood pressure. Subsequent studies in cats using phenyl diguanide and capsaicin demonstrated that these effects were due to activity of vagal endings in the heart (coronary chemoreflex) and the lungs (pulmonary depressor chemoreflex). In 1871 Hering demonstrated that moderate inflation of the lungs of dogs caused a reflex increase in heart rate and that insufflation with higher pressures resulted in bradycardia. A reflex from the lungs affecting the systemic blood vessels was first described by Brodie and Russell, who showed in the cat that a sudden change in the pressure of the respired air from atmospheric to a positive or negative pressure caused a fall in systemic arterial blood pressure that was approximately proportional to the change in air pressure. They concluded on the basis of plethysmographic studies that this was caused by vasodilatation and was reflexly induced, as it was abolished by division of the pulmonary branches of the vagus nerve. These studies provided a stimulus to analyze the role of the lung in the reflex regulation of the cardiovascular system.

Lung-inflation, Systemic Depressor Reflex

Inflation of the Lungs

In dogs in which the systemic circulation was perfused at constant blood flow, and the pressure in the isolated perfused carotid sinuses and aortic arch and the arterial Po2 and Pco2 were kept constant, a maintained inflation of the lungs with air caused a decrease in systemic arterial blood pressure. The magnitude of the dilatation of the systemic resistance vessels varied directly with the pressure and volume of gas used to inflate the lungs. Similar effects were noted when an intermittent positive pressure was applied. The vasodilatation was mediated by reduction in sympathetic adrenergic outflow and the afferent fibers ran in the cervical vagosympathetic nerves and through the stellate ganglia. The threshold inflation pressure to evoke this reflex was 5.5–10.5 cm H2O and occurred with changes in lung volume within the physiologic range. Such studies imply that the lungs are a constant source of afferent impulses that inhibit the vasomotor center and that a lung-inflation, systemic vasodilator reflex may be a factor operating in eupneic breathing. A bradycardia and a negative inotropic response of the ventricles accompanied the systemic vasodilatation. A similar vasodepressor reflex can also be elicited in rabbits, with a threshold of 2.5 cm H2O inflation pressure.

The lung-inflation, systemic depressor reflex was accompanied by inhibition of respiration (Hering-Breuer reflex). Both effects are mediated by slowly adapting pulmonary stretch receptors and are prevented by cooling the cervical vagi to about 8°C. This implies that, like the Hering-Breuer reflex, the majority of the afferent vagal fibers for the depressor reflex are medullated. However, this requires further investigation.

In contrast to these studies, tachycardia was observed during inflation of a normally perfused lung in dogs with moderate pressures, with, if anything, a small reflex increase in vascular resistance in the hindlimb. Sometimes there were negative inotropic responses, but in dogs that showed a reflex increase in heart rate, the inotropic state of the heart was unchanged. Bradycardia and systemic vasodilatation occurred only when the normal reflex activity of the lung was altered as a consequence of artificial perfusion or hyperinflation. Despite the variable and different circulatory responses obtained by varying the conditions in the same dog, inflation of either lung in all experiments consistently resulted in inhibition of respiratory efforts. This raises the question of whether the receptors responsible for the Hering-Breuer reflex are different from those that trigger the circulatory changes.

Interruption of Afferent Vagal Traffic

Another approach to the role of lung receptors in circulatory control is to study the effects of interruption of afferent vagal traffic. When the influence of the arterial baroreceptors is eliminated, blockade of the cervical vagi by cooling in the anesthetized cat, rabbit and dog results in a rise in blood pressure, tachycardia and constriction of the resistance vessels of skeletal muscle, intestine and kidney, and of the splanchnic capacitance bed. There is, however, no change in the tone of the cutaneous veins. The vasoconstriction is unaffected by atropine or section of the vagi at the diaphragm and is caused by an increase in sympathetic adrenergic activity. Thus, in the cardiopulmonary region subserved by vagal afferents there are receptors that exert a tonic inhibition on the central neurons controlling the sympathetic outflow to resistance and capacitance vessels, with the exception of the cutaneous veins.

To determine whether all or only parts of the cardiopulmonary region are involved in the tonic vasomotor inhibition, cardiopulmonary bypass was instituted in anesthetized sinoaortic denervated dogs with diaphragmatic vagotomy. In one study, the heart was removed, leaving the ventilated lungs; in another, the lungs and the ventricles were removed, leaving the beating atria perfused via the coronary arteries; and in a third, the lungs were removed and the atria were denervated, leaving the working innervated ventricles. In each situation, vagal cooling resulted in an increase in aortic blood pressure (fig. 1). Thus, receptors in the lungs, the atria and the ventricles are each responsible for a vagally mediated tonic inhibition of the vasomotor center.

The tonic vasomotor inhibition exerted on both the hindlimb and the kidney resistance vessels by the pulmonary afferents was related to the ventilatory volumes and pressures and was also present during apnea when the lungs were collapsed at atmospheric pressure. This implies that this reflex has a low threshold. These findings are consistent with those of the earlier studies in which lung inflation was used to excite the vagal afferents but are hard to reconcile with the observations of Hainsworth. The following observations illustrate both the potential of pulmonary receptors to influence the cardiovascular...
system in conscious, naturally respiring dogs and the difficulties in dissecting the mechanisms involved. During recording sessions with the dogs lying quietly, they would, at intervals, give what can best be described as a deep sigh. The accompanying responses of heart rate and arterial blood pressure are illustrated in figure 2. With the beginning of inspiration there was a brief tachycardia that lasted 8-10 seconds and was followed by a transient, profound bradycardia. Tachycardia was accompanied by an increase in arterial pressure of 20 mm Hg; bradycardia, by a fall of 50 mm Hg. These responses also were observed during arterial hypertension induced by carotid sinus hypotension (40 mm Hg), but were smaller. They were observed during the bradycardia and hypotension resulting from elevation of pressure within the vascularly isolated carotid sinus (from 40 to 145 mm Hg). Atropine abolished the changes in heart rate and the initial rise in pressure; the decrease in pressure was still present, but was reduced. The contribution to these responses of activation of lung and cardiac receptors and of impulses arising centrally is not known.

Receptors in the atria and ventricles are involved in the neural control of renin secretion, by causing changes in sympathetic outflow to the kidneys. Reflexes from the lungs also can alter this outflow, so it is likely that they are also involved, but direct proof of this is lacking.24

Medullated vs Nonmedullated Vagal Afferents

Attempts have been made in rabbits and cats to analyze the role of medullated and nonmedullated vagal afferents in this tonic vasomotor inhibition. During normal ventilation, slowly adapting pulmonary stretch receptors with medullated afferent vagal fibers (mean conduction velocity 32 m/sec) show spontaneous activity in concert with inflation of the lungs.26 These receptors, which are thought to lie in and around airways, serve the classic inhibitory respiratory reflex described by Hering and Breuer.5 In addition, electrophysiologic studies have demonstrated an extensive system of afferent vagal C-fibers (conduction velocity less than 2.5 m/sec) in the heart, lungs, great vessels and abdominal viscera.26 In anesthetized rabbits with sinus and aortic nerves cut, cooling of the cervical vagi to 12, 8, 6 and 0°C causes progressive increases in aortic blood pressure. The activity in medullated fibers is blocked at 6°C, and this implies that the increase in pressure on vagal cooling from 6°C to 0°C (40% of the total increase in pressure) must be due to blockade of spontaneous activity in the nonmedullated fibers.27 In cats, anodal block of medullated fibers was induced by application of a DC current to the cervical vagus, under circumstances in which there was no evidence for simultaneous activation or blockade of nonmedullated fibers. The left vagosympathetic trunk, the right aortic nerve and both carotid sinus nerves were cut. In nine cats with the anodal block alone, there was a mean increase in pressure of 8 mm Hg; interruption of all afferent vagal traffic by cooling caused a mean increase in aortic blood pressure of 38 mm Hg. Thus, 80% of the increase could be ascribed to interruption of traffic in nonmedullated fibers.28

While the aggregate of the total afferent vagal inhibitory input to the vasomotor center from the thoracic viscera appears to involve predominantly nonmedullated afferents, these studies do not separate

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**Figure 1.** Vascular responses to vagal cold block before and after removal of the lungs. Dog on cardiopulmonary bypass, with arterial baroreceptors denervated, vagi cut at diaphragm, and the heart removed. One hindlimb and kidney perfused at constant pressure of 120 mm Hg. Cooling the cervical vagi to 0°C with the lungs artificially ventilated caused an increase in aortic blood pressure and a decrease in renal and hindlimb blood flow. Removal of the lungs resulted in an increase in aortic pressure and a decrease in renal and hindlimb blood flow (RF and HL). There was no further change with vagal cooling. (From Mancia G, Donald DE: Circ Res 36: 310, 1975. Reproduced with permission.)
the contributions of the lungs and heart and thus still leave in question the afferent fiber types responsible for the lung-inflation depressor reflex.

Changes in Sympathetic Outflow

Comparisons have been made in animals of the relative influence of the cardiopulmonary and carotid sinus receptor systems on the sympathetic outflow to different vascular beds. At low levels of activation of both receptor systems, the sympathetic outflow to muscle vessels appears to be equally affected by both sets of receptors; at moderate and high levels of activation, muscle vasomotor fibers are less inhibited by cardiopulmonary than by carotid baroreceptors. At low levels of activation, the renal vasomotor fibers appear to be more inhibited by the cardiopulmonary than the carotid baroreceptors, whereas the renal vasomotor fibers respond equally to high levels of activation of both systems. In closed-chest dogs with their aortic nerves sectioned and their carotid sinus pressure controlled, combined withdrawal of carotid and cardiopulmonary inhibition decreased hindlimb and renal blood flow by about 80% and 40%, respectively, during both normovolemia and hypervolemia. Interruption of cardiopulmonary inhibition was responsible for 17% and 31% of the decrease in hindlimb blood flow at normal and increased blood volumes, respectively; values for the decreases in renal blood flow were 50% and 65%. Thus, cardiopulmonary receptors oppose the vasoconstriction due to carotid sinus hypotension more effectively in the kidney than they do in the hindlimb.

However, the separate role of cardiac vs lung receptors in these responses has not been defined. In the anesthetized dog, mechanically ventilated and with sinoaortic denervation, the reflex control of hindlimb and renal resistance vessels by cardiac and pulmonary receptors was studied by interrupting afferent vagal traffic when only the heart or only the lungs were in situ. The inhibition exerted by the heart and lung receptors on these two beds were similar during normocapnia but were greater on the renal vessels during hypercapnia. However, this augmentation was significant for the heart-only preparation.

Hypercapnia

In the rabbit during hypercapnia and vagal block, the muscle resistance vessels constrict, but much less than those in the kidney (fig. 3). This powerful constriction of the renal vessels was accompanied by a marked increase in activity in the renal sympathetic nerves. Studies during diffusion respiration demonstrate that the vasoconstriction resulting from the hypercapnia can be annulled by lung inflation, partic-
ularly in the kidney (fig. 4). In other studies in spontaneously breathing rabbits, the effect of hypercapnia was studied with both increased ventilation (caused by inspiration of mixtures of carbon dioxide in oxygen) and decreased ventilation (caused by inflation of gallamine triethiodide during oxygen breathing). The increase in renal vascular resistance caused by vagal block during hypercapnic hyperventilation was six- to sevenfold greater than in normocapnic normal ventilation. A similar augmentation of the response to vagal block was seen during hypercapnic hypoventilation (fig. 5). Thus, the powerful central constrictor effect of carbon dioxide can be counteracted in the renal vasculature by vagal afferents activated by lung movement; even minimal respiratory movements, which make little or no contribution to respiratory gas exchange, can activate the pulmonary receptors responsible for the inhibitory reflex.  

In the anesthetized, mechanically ventilated rabbit with the carotid sinuses denervated and the vagi

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**Figure 3.** Effect of hypercapnia on circulatory changes caused by vagal cold block in a rabbit with its sinus and aortic nerves cut. (top) Temperature of thermodes and intratracheal pressure. (bottom) Aortic blood pressure, kidney and hindlimb perfusion pressure and right atrial pressure. Kidney and hindlimb were perfused at constant flow with autologous blood. Note the marked increase in kidney perfusion pressure compared with the increase in hindlimb pressure during hypercapnia, due to the strong constriction of the renal resistance vessels. (From Ott NT, Shepherd JT: Circ Res 33: 160, 1973. Reprinted with permission.)

**Figure 4.** Effect of lung inflation on kidney perfusion pressure in rabbit with carotid sinus and aortic nerves cut. Kidney was perfused at constant flow with autologous blood; thus, changes in perfusion pressure were caused by constriction or dilatation of kidney resistance vessels. The rabbit was ventilated artificially with oxygen. Stopping the ventilation (upper dotted line) caused a small increase in perfusion pressure (lower dotted line) and a larger rapid increase after about 1 minute. Inflation of the lungs twice to 10 cm H2O during cessation of ventilation (upper solid line) caused a decrease in perfusion pressure (lower solid line). The first inflation (at relatively low PaCO2) caused a small decrease in kidney perfusion pressure, whereas the second inflation (at a higher PaCO2) caused a marked decrease. With resumption of artificial ventilation, perfusion pressure decreases rapidly. After vagotomy (not shown) with resumption of ventilation the pressure only decreases slowly. (From Shepherd JT: Circulation 50: 418, 1974. Reprinted with permission.)
Shepherd JT. and (3) hypercapnic hyperventilation symbols), control conditions hypoventilation induced by autologous blood. Hindlimb and kidney perfusion with carbogen breathing simultaneously, of particular the inhibitory parasympathetic afferents. Holmes and Torrance observed afferent fibers that pass through the stellate ganglion to the spinal cord and can be stimulated by lung inflation. Some mechanoreceptors in the lung parenchyma are subserved by medullated fibers (Aδ type), which pass in the sympathetic nerves to the spinal cord and increase their discharge with inflation of the lung. The receptor threshold value was approximately 1 mm Hg and discharge frequency increased linearly with an increase in tracheal pressure, 0.8 Hz · mm Hg⁻¹.

Diving Reflex

Mammals (including man), birds, and reptiles have the ability to redistribute their circulation during diving. This is caused by activation of two reflexes. When the face is immersed in water, the sensory endings of the trigeminal nerve are activated. This elicits a reflex cessation of respiration, vagal-induced bradycardia, and constriction of systemic vessels in the splanchnic region, skeletal muscles and kidneys due to an increased activity of their sympathetic nerves. The splanchnic and cutaneous capacitance vessels constrict. The apnea is followed quickly by a decrease in PO₂ and an increase in PCO₂ in the arterial blood, which stimulates the arterial chemoreceptors. The continued sensory input from the trigeminal nerve overrides the action of the chemoreceptors on the respiratory center. The circulatory effects of chemoreceptor stimulation augment those from the nose and face, leading to further cardiac slowing and constriction of systemic vessels. There is a reflex dilatation of the coronary arteries mediated by the vagal nerves. Thus, the annulment of the pulmonary depressor reflex by the reflex respiratory arrest permits the full expression of these other reflexes, so that the arterial blood pressure is maintained and the oxygen in the blood is made available to the most vulnerable systems, the heart and brain.

Other Respiratory Reflexes

Receptors with Medullated Vagal Afferents

Another type of receptor, stimulated by hyperinflation and forced deflation of the lungs of dogs, is innervated by medullated afferent fibers (conduction velocity 23 m · sec⁻¹), but, in contrast to the classic pulmonary stretch receptor, rapidly adapts to the distorting stimulus. The most consistent method of exciting these receptors apart from hyperinflation is blocked, hypercapnia augments the vasomotor inhibition of renal and skeletal muscle vessels exerted by the aortic arch baroreceptors, the effect on renal resistance being more pronounced. Thus, this phenomenon appears to be a general property of reflexes that tonically inhibit the vasomotor center. Carbon dioxide probably acts centrally to accentuate particularly the inhibitory control of the renal vessels by the vagal and other inhibitory afferents, thus countering the central excitatory effects of carbon dioxide. The preservation of renal blood flow through this mechanism would obviously contribute to the restoration of acid-base balance in respiratory acidosis.

Role of Lung-inflation Reflex in Modulation of Other Reflexes

Chemoreflexes

During carotid chemoreceptor stimulation, in both conscious and anesthetized dogs, associated increases in ventilation attenuate the chemoreceptor-induced bradycardia and peripheral vasoconstriction. In the conscious dog, nicotinic stimulation of the carotid chemoreceptors causes dilatation of the coronary vessels due to withdrawal of sympathetic α-adrenergic activity. A minor part of this comes from the chemoreflex and the major part from the increase in depth of respiration. A similar vasodilatation can be seen with forced mechanical or spontaneous hyperinflation in the conscious dog. A mystery is that the coronary dilatation is little attenuated by vagotomy. Glick et al. noted that the systemic responses to inflation of the lungs are not entirely abolished by vagotomy. A possibility is excitation of pulmonary receptors with sympathetic afferents. Therefore, the carbon dioxide technique is a powerful tool for investigating and understanding the neural control of cardiorespiratory function.
exposure to histamine. Irritant substances such as ammonia, ether and cigarette smoke do not cause an increase in receptor activity. Rapidly adapting pulmonary receptors with medullated afferent vagal fibers (mean conduction velocity 12.9 m/sec) also have been described in the rabbit. During normal respiration the spontaneous discharge is sparse, irregular and often unrelated to the respiratory pattern. Inhalation of irritant vapors and i.v. injections of histamine increase receptor discharge. Anaphylaxis and microembolism of the lung also are effective.

In contrast to the classic pulmonary stretch receptors, no physiologic role for these receptors has been demonstrated. They may be involved in the reflex hyperpnea, which attends pneumothorax and pulmonary congestion, and in the bronchoconstriction of anaphylaxis and pulmonary microembolism. However, mechanoreceptors located elsewhere in the thoracic cavity (esophagus, pulmonary artery) increase their discharge on exposure to similar ventilatory and chemical stimuli. This emphasizes the care that must be taken in identifying the receptors claimed to cause a particular reflex. Fishman et al. proposed that the normal pattern of breathing in the conscious dog may depend on a balance between the opposing effects on respiration of two vagal reflex mechanisms: one that is "respiratory-inhibitory" and the other "respiratory-stimulating," both of which are stimulated during eupneic breathing. The respiratory-inhibitory is blocked over the same range of temperatures during vagal cooling that the Hering-Breuer inflation reflex is blocked. The respiratory-stimulatory is blocked at a lower temperature, and it might be the irritant reflex. The interaction of these two reflexes may be one of the mechanisms by which an optimal respiratory frequency is achieved.

Receptors with Nonmedullated Vagal Afferents

Coleridge and Coleridge characterized the vagal C-fiber endings in the lungs according to the vascular route by which they are accessible to chemicals injected into the bloodstream. Thus, pulmonary C-fiber endings, which include the juxtapulmonary capillary receptors, are accessible through the pulmonary circulation. In cats, these endings appear to be the only receptors in the lungs capable of initiating the pulmonary depressor chemoreflex. Bronchial C-fiber endings, many of which are in the intrapulmonary airways, are those accessible through the bronchial circulation. The juxtapulmonary capillary receptors were initially called deflation receptors, in the belief that this was their natural stimulus. Later evidence indicated that they were localized in the interstitial space of the lung at the alveolar level, and they were renamed "J" receptors. The spontaneous activity of these receptors is sparse and irregular and shows no respiratory modulation at normal ventilatory volumes. The receptors are stimulated by hyperinflation, but the resultant patterns of activity vary considerably; some animals show irregular bursts and others a continuous discharge, which then either increases or decreases with further distention of the lung. It has been suggested that the natural stimulus to the nonmedullated vagal receptors is pulmonary congestion. These receptors therefore may be involved in reflex bradycardia and tachypnea, which accompany this condition, and could be an important source of dyspnic sensations associated with pulmonary edema. They also bring about a depression of the somatic nervous system, which is manifest by a loss of muscle tone and an inhibition of muscle reflexes. Moderate exercise at altitude results in substantial increases in pulmonary capillary pressure and, occasionally, in pulmonary edema. In these circumstances, increased activity of J receptors might cause inhibition of the exercise, possibly by reflexly depressing the traffic in the motor nerves to working muscles.

Pulmonary Artery Mechanoceptors

Baroreceptors linked to vagal afferents are present in the pulmonary artery of dogs at or beyond the bifurcation. Distention of the pulmonary artery evokes two opposing reflex mechanisms. In some dogs, pulsatile distention, with pressures between 20–60 mm Hg, causes systemic hypotension and, occasionally, bradycardia mediated by the pulmonary arterial baroreceptors. With pulsatile distention greater than 80 mm Hg, despite augmentation of pulmonary baroreceptor discharge, the systemic pressure increases. Thus, the inhibitory effect has been overcome by a more powerful pressure response. Both pressor and depressor responses were abolished by vagotomy. Afferent fibers in the left cardiac sympathetic nerve innervating mechanosensitive receptors in the wall of the pulmonary artery of cats have also been described. These receptors probably are not active at the pressures normally present in the pulmonary arterial circulation, but signal only a transient rise in pressure.

Cardiovascular Reflex from the Lungs in Man

Dr. Richards' research interests were in elucidation of cardiopulmonary function in man, so it is fitting to end with the very limited information available.

Evidence for Lung Receptors

The injection of phenyl diguanide or sodium cyanide into the main pulmonary artery of patients referred for investigation of lung function caused a stimulation of breathing, together with bradycardia and hypotension. Analysis of the mean injection-response time indicated that these drugs were acting on the carotid body rather than on receptors in the lungs. In contrast, lobeline sulphate caused apnea before hyperpnea. The former was attributed to stimulation of pulmonary receptors before excitation of the carotid bodies, indicating that there are receptors in the human lung that are depolarized by chemical agents.
Response to Lung Inflation

A reflex inhibition of respiration occurs in man with large lung inflations, but not at normal tidal volume. Thus, the Hering-Breuer reflex appears to be less potent in humans than in animals. Electrical stimulation of vagal afferents caused a fall of arterial blood pressure. However, this was attributed to impairment of venous return and, hence, in cardiac output caused by the accompanying mechanical changes in the chest associated with coughing. In five patients studied during cardiopulmonary bypass, lung inflation had no effect on heart rate or total peripheral resistance. These negative results might be attributed to insufficient inflation of the lungs, to the halothane anesthesia, or to the low $P_{CO_2}$.

Respiratory Sinus Arrhythmia

The increase in heart rate during inspiration and the slowing during expiration, which is most marked in children and young adults, is caused by a variation in the depolarization frequency of the sinus node, caused largely by alteration in vagal activity. Four mechanisms could explain the increase in heart rate with inspiration: (1) reflex inhibition of the cardioinhibitory center (vagal nucleus) by the slowly adapting stretch receptors in the lungs; (2) central irradiation of inhibitory impulses from the respiratory centers to the cardioinhibitory center; (3) increased filling of the right atrium during inspiration, which activates mechanoreceptors at the junction of the great veins with the right atrium, increasing sympathetic activity to the sinus node; and (4) a change in sensitivity of the carotid sinus baroreflex occurring in phase with the respiration. Baroreceptor stimuli applied during early and midinspiration and late expiration cause only minor inhibition of the sinus node; stimuli during late inspiration and early expiration cause maximum inhibition. An elevation of the set point of the carotid sinus baroreflex also would permit an increase in heart rate and arterial pressure; lowering of the set point during expiration would allow depression of rate and pressure.

During inspiration, chemoreceptor effects on the heart rate also are blocked. The respiratory modulation of the carotid chemosensitive and baroreflexes is attributed both to an inhibitory effect on the reflexes arising from activity of inspiratory neurones in the central nervous system and from the excitation of intrapulmonary receptors during air flow into the lungs.

When blood is displaced from the central circulation to the lower parts of the body, there is a reflex constriction of the resistance blood vessels in the forearm and splanchnic bed. This still occurs when the displacement is too small to alter the arterial blood pressure, arterial $dP/dt$ or heart rate. When blood is displaced from the legs to the central circulation, a reflex dilatation of the forearm vessels occurs again in the absence of any evidence of a change in signal to the arterial baroreceptors. Thus, these reflex vascular changes have been attributed to mechanoreceptors in the heart and lungs. Thus, the cardiopulmonary receptors in man appear to be as important as the arterial baroreceptors in determining peripheral resistance in situations where there is a moderate reduction in circulating blood volume. Also, during space flight, when zero gravity is reached, the blood from the lower body is displaced to the upper part of the body. The vascular resistance in the legs is decreased. The hemodynamic and humoral adjustments are probably a consequence of changes in the activity of the cardiopulmonary mechanoreceptors.

While the cardiac receptors probably have the primary role in these responses, receptors in the lungs might contribute. It is difficult in animals to separate the role of receptors in the lungs from those of the heart in the regulation of the circulation; it will be a much greater challenge to achieve this in man.

Deep Breath Reflex

While the reflexes from the heart and lungs and the arterial baroreflex in animals and man do not affect the sympathetic outflow to the cutaneous veins, these veins, together with the resistance vessels to the digits, constrict strongly in man in response to a deep breath. The constriction is caused by a spinal reflex, because it is present in paraplegics with complete spinal cord transection. Obstruction of the airways during either inspiration or expiration causes an increase in tone of the cutaneous veins, but this only occurs occasionally with pressure inflation of the lungs. Cutaneous venoconstriction also occurs in the anesthetized subject breathing 8% carbon dioxide, but not if active respiratory movements are prevented by muscle relaxants. Hence, neither emotion nor stretch receptors in the lungs are responsible, and the afferent source of this reflex probably is in the chest wall or diaphragm.

In the closing part of his Nobel lecture, Dr. Richards looked to the future and to areas where further basic research should be concentrated. In this regard, the circulatory reflexes originating in the heart and lungs continue to present a challenge. Efforts must be made not only to define their roles, the nature of the receptors, their afferent pathway and central connections, but also to determine whether reflexes that originate in the lungs are of physiologic consequence and are involved in disease states or whether they are curiosities to be activated only by foreign substances or in the abnormal circumstances induced by complex laboratory procedures.

References

2. Paintal AS: Vagal sensory receptors and their reflex effects. Physiol Rev 53: 159, 1973
4. Widdicombe JG: Reflex control of breathing. In MTP International Review of Science, Physiology Series 1, vol 2, Respiratory Physiology, edited by Widdicombe JG. Baltimore, Univer-
CO₂ in spontaneously breathing rabbits. Am J Physiol 228: 530, 1975
34. Daly M, Hazzledine JL: The effects of artificially induced hyperinflation on the primary cardiac reflex response to stimulation of the carotid bodies in the dog. J Physiol (Lond) 168: 872, 1963
47. Paintal AS: The location and excitation of pulmonary deflation receptors by chemical substances. Q J Exp Physiol 42: 56, 1957
51. Coleridge JCG, Kidd C: Reflex effects of stimulating baroreceptors in the pulmonary artery. J Physiol (Lond) 166: 197, 1963
57. Haymet BT, McCloskey DJ: Baroreceptors and chemoreceptor influence on heart rate during the respiratory cycle in the dog. J
Physiol 245: 699, 1975


Davidson NS, Goldner S, McCloskey DI: Respiratory modulation of baroreceptor and chemoreceptor reflexes affecting heart rate and cardiac vagal efferent nerve activity. J Physiol (Lond) 259: 523, 1976


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