Clinical Significance of Reflexes from the Respiratory System

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The extensive literature on respiratory reflexes is notably lacking in information about the reflexes in humans, whether healthy or diseased. The reflexes have usually been studied by experiments with nerve transections, with recordings of action potentials from dissected nerves, or with operative isolation of the sites of origin or motor action of each reflex, and such methods have seldom been practical for man. Of necessity, therefore, this review will deal mainly with experiments on animals; evidence, largely by analogy, for similar mechanisms in man will be discussed; the possible role of the reflexes in abnormal or pathological conditions is usually a matter of speculation.

There is a second reason why many conclusions must be tentative: the animal experiments may impose an illusion of simplicity. In intact man and animals activation of a reflex may involve several afferent pathways, and the motor response will change lung volume, ventilation rates, blood gas tensions and cardiovascular conditions, each of which will secondarily modify respiration via reflexes. Respiratory reflex action has seldom been assessed quantitatively, and the complex interaction of reflexes in intact man has not been unravelled. Reference may be made to more detailed reviews where some of these complexities are considered.12, 25, 28, 44, 109, 120, 124, 122, 128, 125, 180

Lung Inflation Reflexes

The Hering-Breuer Inflation Reflex. In 1868 Hering and Breuer71, 63 showed that inflation of the lungs inhibits diaphragmatic contractions, and the reflex has since been described for many mammalian species including man.25, 130 In anesthetized animals small inflations decrease the frequency of inspiratory efforts, while larger ones completely abolish them until asphyxic stimulation breaks through. In some species expiratory muscle contractions are augmented,116, 121 but this is usually a weak or exceptional reaction.1, 122

The afferent end-organs for the reflex lie in the walls of the airways, from the larynx probably as far as the bronchi, (fig. 1). On histological17, 56, 67, 52, 53 and physiological37, 129, 131 evidence there are receptors in the smooth muscle. In 1933 Adrian1 showed that they respond primarily to lung volume changes, with a slowly adapting discharge. However this discharge is secondarily modified by changes in the mechanical properties of the lungs, being augmented by pulmonary vascular congestion,49 edema or collapse,51 and being also influenced by the rate of change of lung volume.27 The receptors have afferent fibers in the vagus nerves, vagotomy preventing the reflex actions. Many of the receptors have a tonic discharge at functional reserve capacity (FRC) level.1

The physiological role of the inflation reflex is complex. Since the receptors inhibit inspiration, their tonic discharge may depress the level of activity of the respiratory center. Vagotomy, which abolishes other reflexes as well as the inflation, has variable effects on alveolar ventilation rate,122 but the careful study of Lim et al.83 indicates that removal of vagal tone increases alveolar ventilation of anesthetized dogs by about 30 per cent. The reflex may set the volume level of breathing,121 potentiation of the reflex decreasing the end-expiratory level, at least in animals without an expiratory pause.121

The reflex control of the breath-to-breath pattern of breathing has been studied most frequently. Abolition of the inflation reflex slows and deepens breathing103, 122, 126 since the normal role of the reflex is to cut sho
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Fig. 1. Diagram of afferent and efferent nerves for respiratory reflexes from the respiratory system; greatly simplified.

Each breath and thus to limit inspiration and thereby increase the frequency of breathing. Otis, Fenn, and Rahn showed that the pattern of breathing determines the mechanical work of ventilating the lungs for any given alveolar ventilation rate, and Christie indicated that the rate and depth of breathing are adjusted to minimize work for different mechanical conditions of the lungs in various physiological and pathological states. Mead believes that average respiratory muscle force is minimized in a similar way. These workers have suggested that the inflation reflex may be the agent for the adjustment of breathing to the optimal frequency; certainly receptor activity and reflex action are changed in pulmonary vascular congestion, edema and collapse, and possibly in bronchoconstriction, in such a way as might adjust breathing to an economical pattern in terms of mechanical work or muscle force. Other reflexes may also be involved.

Lung inflation not only inhibits inspiratory activity, but probably has a reflex action on the airways, decreasing tracheobronchial smooth muscle tone. Inflation also affects the cardiovascular system, usually increasing heart rate and constricting the systemic vascular bed (although the opposite has also been described) (table 1).

The afferent mechanism for these autonomic reflexes has not been established, but the inflation reflex is possible. In man the inspiratory inhibition due to lung inflation is weaker than for other mammals, and it may be absent in unanesthetized subjects. However, the reflex has not been sought in hyperpnea or clinical conditions. In man the rate of breathing alters in response to changes in lung compliance or resistance, the belief that this is due to the inflation reflex is based solely on analogy with animal work. During a bronchoconstriction transient inflation of the lungs increases airway caliber for about one minute, and in clinical bronchoconstriction this could be a beneficial result of the increased FRC, although passive distension of the airways may be more important than reflex dilatation. Lung inflation causes systemic vasoconstriction in man, with the sensitivity of the respiratory center to blood gas tensions, since a large inflation may permit arterial P_{CO_2} to surpass 90 mm. of mercury before breath-holding becomes intolerable. With paralyzed patients the awareness of blood P_{CO_2} changes is enhanced by decreases in tidal volume.

These observations indicate that the pattern of artificial ventilation or of other proce-
### Table 1. Summary of Motor Effects of Reflexes From the Respiratory System

<table>
<thead>
<tr>
<th>Reflex</th>
<th>Respiratory</th>
<th>Blood Pressure</th>
<th>Heart Rate</th>
<th>Bronchodilator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hering-Breuer Inflation</td>
<td>Inspiratory inhibition</td>
<td>? Hypertension</td>
<td>? Tachycardia</td>
<td>? Dilation</td>
</tr>
<tr>
<td>Hering-Breuer Deflation</td>
<td>Inspiratory stimulation</td>
<td>? Hypotension</td>
<td>? Bradycardia</td>
<td>? Constriction</td>
</tr>
<tr>
<td>Head's Paradoxical Inflation</td>
<td>Inspiratory stimulation</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Nasal Irritation</td>
<td>Anaesthesia</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Tracheal Mechanical Irritation</td>
<td>Cough</td>
<td>Hyperpnea</td>
<td>? Hypotension</td>
<td>? Bradycardia</td>
</tr>
<tr>
<td>Pulmonary Chemical Irritation</td>
<td>Hyperpnea</td>
<td>Hypotension</td>
<td>Bradycardia</td>
<td>Constriction</td>
</tr>
<tr>
<td>Multiple Pulmonary Embolism</td>
<td>Apnoea and rapid shallow</td>
<td>Hyperpnea</td>
<td>Bradycardia</td>
<td>Constriction</td>
</tr>
</tbody>
</table>

Decreses altering lung volumes may reflexly modify the sensitivity and activity of the respiratory center, and may also influence airway smooth muscle tone and the cardiovascular system. It must be remembered, too, that volatile anesthetics first enhance and then inhibit the receptors for the reflex; this is a local action. The reflex persists in deep barbiturate anesthesia.

**Head's Paradoxical Reflex.** Until recently this has been a curiosity ever since Head showed that large inflations of the lungs augment diaphragmatic contractions if the opposing activity of the Hering-Breuer inflation reflex is prevented. The reflex is vagal and of considerable power in the rabbit, but the afferent end-organs have not been identified, although they lie in the lungs and not the extrapulmonary airways. It has been suggested that one role of the reflex is to cause the occasional deep breaths seen in most mammals; these breaths are thought to reverse any tendency to alveolar collapse in quiet breathing. Lately Cross et al. have shown that the newborn baby gasps when its lungs are inflated, which would be beneficial in helping to aerate the lung. For the adult it would be interesting to see if inflation of collapsed lung initiates the paradoxical reflex, thus tending to overcome the collapse. In anesthetized animals there is progressive collapse of lung, reversible by inflation, but the reflex has not been demonstrated in adult man, possibly through lack of careful attempt.

**Lung Deflation Reflexes**

Deflation of the lungs will stimulate breathing by lessening the tonic discharge of receptors for the Hering-Breuer inflation reflex. However, there is evidence of a deflation reflex with separate receptors and vagal fibers, whose activity increases the respiratory rate or inspiratory force or both. Pintall has studied receptors in the cat which respond to deflation, and concludes that they mediate the deflation reflex and are also responsible for the bradycardia and hypotension which follow injection of certain drugs into the lungs. Bronchoconstriction may also be a component of the reflex, although this is not established. The receptors probably lie in the walls of the finest air passages or of the alveoli, where they would be best situated to respond to collapse.

The deflation reflex might be supposed to reverse lung collapse, but in most animals lung deflation increases the rate of breathing rather than the depth; there is also clear hyperventilation, so the reflex could compensate for blood gas changes due to lung collapse rather than re-aerate the lung. Anesthetized animals with complete cessation of breathing due to anesthesia can be maintained alive by the reflex respiratory stimulus of chest compression.

With unanesthetized man deflation of the lung stimulates breathing, but not conspicuously. Collapse of the lung due to pneumo-
thorax causes hyperventilation,19, 27 since CO2 tensions fall,26, 113 and chest compression and negative pressure breathing might be expected to cause a similar effect.

It will be apparent that the inflation and deflation reflexes present a therapeutic difficulty to the clinician, for the more effective stimulus to breathing is a decrease in lung volume which may limit the degree of pulmonary aeration; that changes in lung volumes also alter cardiovascular and bronchomuscular conditions, both mechanically and reflexly, in an ill-defined way, introduces a further problem which has not been adequately assessed. A large number of drugs can inhibit and then increase the rate of breathing by stimulation of pulmonary receptors,35, 30 possibly deflation endings.106, 107 These drugs have reflex cardiovascular39 and bronchomotor actions,10 but few of them have been tried in man. Many volatile anesthetics may belong to this group and activate the deflation reflex.125

Irritation of the Respiratory Tract
The Nose. A variety of stimuli can elicit respiratory reflexes from the nose,132, 135 for example smoke,78 chemical irritants,5, 41 cold air or water,46, 109 or touch to the mucous membrane.8, 90, 111 In anesthetized animals these stimuli usually depress breathing (although occasionally hyperpnea occurs4, 41) with hypertension and bradycardia;65 the last could be secondary to the blood pressure rise via the baroreceptor reflex. The reflex changes in breathing can be induced by chemicals, such as peppermint, coffee and asafetida,3 which are odors rather than irritants.5, 3 Sneezing has seldom been observed in experiments, presumably because it is readily blocked by anesthetics, in this way differing from the cough reflex. Nasal irritation conspicuously depresses skeletal muscle tone and reflexes.8, 53 Of greater physiological relevance is the fact that an airstream in the nose reflexly stimulates breathing, sometimes with a preceding apnea.8, 111 Repetitive puffs of air in the nose can set the pace of breathing after vagotomy.111

Nasal irritation also causes spasm of the glottis and bronchoconstriction.31, 45, 76, 90, 108, 124, 123 Although these effects have usually been studied with strong chemical irritants or smoke, they also follow mechanical stimulation and cold air, but have not been established as a reflex response to airflow.

All these reflexes are conducted in the olfactory and trigeminal nerves,4 and the afferent end-organs have not been identified.

Nasal reflexes have not been studied much in man, but insertion of cold saline or water into the nose causes apnea and hypertension.46 Inhaled cold air constricts the bronchi of asthmatics, but not appreciably of normals, presumably by a reflex from the upper respiratory tract.126 However, if human beings have similar reflexes to the experimental animals, mechanical stimulation of the nasal mucous membrane, as by a perinasal tube, will activate respiratory, bronchomotor and cardiovascular reflexes.

The Larynx. The reflex effects of laryngeal irritation are similar to those of the nose, with the exception that the expiratory efforts of coughing may be prominent. The larynx is exceptionally sensitive to mechanical irritation,36, 60, 81, 128 the reflex response including laryngospasm,72 bronchoconstriction75, 128, 133 and cardiac arrhythmias.24 Both the epiglottis40 and the laryngeal mucous membrane9 are abundantly supplied with afferent end-organs and may be the main site of origin of these reflexes. Distension of or airflow through the larynx can activate receptors and lead to apnea and bradycardia,102 There is little experimental work with man, probably because the larynx is locally anesthetized before irritation, in order to prevent coughing and reflex spasm.

The Trachea and Bronchi. The lower respiratory tract has afferent end-organs whose terminations ramify between the epithelial cells and reach nearly as far as the ciliary layer.47, 55, 67, 52, 92 The receptors are concentrated at the carina and points of bronchial branching, the sites from which the cough reflex can most readily be elicited by mechanical stimuli.61, 126 When stimulated the receptors give a brief discharge of impulses,127 and they are excited by touch, inhaled dusts, even if submicronic,101 and by vigorous volume changes of the airways.127 These stimuli cause coughing, with primary expiratory efforts, and also reflex constriction of the bronchi and glottis.70, 71, 110 Cardiovascular
changes are less well defined. Injection of water into the trachea causes transient apnea and considerable changes in the mechanical properties of the lungs.\textsuperscript{25, 58} In most species the reflexes are mainly vagal, with a small afferent component in the sympathetic nerves. In man the vagal path predominates.\textsuperscript{76}

The mechanical effects of coughing include intrathoracic and cerebrospinal pressure swings of up to 300 mm. of mercury,\textsuperscript{56, 116} up to seven-fold changes, mainly passive, in airway volume,\textsuperscript{41, 62} and increased resistance to expiratory airflow which may lead to airtrapping.\textsuperscript{40} Coughing is effective in tracheotomized patients, so glottis closure is not essential. Active bronchial peristalsis during the expiratory phase of coughing (‘bronchial vomiting’) is certainly not established and has been denied.\textsuperscript{61, 108, 133}

Deeper in the lungs lie receptors which respond primarily to chemical irritants, including volatile anesthetics.\textsuperscript{137} Their reflex action in general corresponds to that of the tracheal endings, especially as regards bronchoconstriction,\textsuperscript{5, 14, 41, 48} but differs in two important respects. First, there is usually hyperpnea or rapid shallow breathing, and the expiratory efforts of coughing may be weak or absent.\textsuperscript{6, 7, 12} Second, both the receptors and reflex tend to accommodate to maintained or repeated stimulation,\textsuperscript{120, 131} which may correlate with the clinical observation that pulmonary debris only causes coughing when it reaches the larger airways.\textsuperscript{40} The response to gaseous irritants is complicated because they may have a direct, nonnervous constrictor action on the airways,\textsuperscript{10} and because a sympathetic nervous component of the afferent pathways is important, at least for some species.\textsuperscript{14, 133} Volatile anesthetics may paralyze irritant receptors after an initial stimulation,\textsuperscript{121} quite apart from any central nervous action on the irritant reflexes.

Interesting studies by Kreuger and Smith have shown that positively charged ions of air constrict airway smooth muscle,\textsuperscript{19} probably by release of 5-hydroxytryptamine,\textsuperscript{80} whereas negatively charged ions inhibit the muscle tone. The importance of this effect in intact animals has not been assessed, nor has the possible role of airway afferent end-organs in the response.

**Irritants in Man.** With man it is usually impossible to determine the site of action of an irritant. An exception is the mechanical stimulation of the larynx or trachea by an endotracheal tube, which constricts the glottis and bronchi,\textsuperscript{72} and also causes cardiac arrhythmias.\textsuperscript{24, 112} Inhalation of ‘inert’ dusts\textsuperscript{30, 45} or cigarette smoke\textsuperscript{40} constricts the bronchi; by analogy with work on animals, this may be reflex. Irritant chemicals such as sulfur dioxide and sulfuric acid cause bronchoconstriction, tachycardia and hyperpnea.\textsuperscript{1, 100} when the gaseous concentrations are probably too low to have an action via the blood stream. It is significant that these effects can occur with concentrations of irritants too weak to cause coughing or even awareness of the irritant; this correlates with indirect evidence for animals that irritant reflex bronchoconstriction has a lower central reflex threshold than coughing,\textsuperscript{120} although the afferent receptors are the same for both responses. Stronger chemical irritants in anesthetized man depress breathing and raise blood pressure.\textsuperscript{4}

In general, therefore, one would expect any mechanical, chemical or thermal irritation of the respiratory tract, from nose to lungs, to change respiration, blood pressure, heart rate and bronchomuscular tone. The magnitude of each change would depend on the stimulus and on the subject or patient. It must be emphasized, too, that the reflex responses may be profoundly modified by local or general anesthesia, and by drugs, such as atropine, acting on the motor pathways of the autonomic nervous system.

**Reflexes from the Pulmonary Vascular Bed.**

Raising the pressure in the isolated or perfused pulmonary vascular bed of experimental animals causes rapid breathing sometimes preceded by apnea.\textsuperscript{11, 12, 43} Tidal volume usually decreases but may increase; in either event minute volume rises. The response, which is a vagal reflex, has recently been studied by Aviado et al.,\textsuperscript{11} who also observed hypotension, and they concluded that the reflex arises from the pulmonary veins. The reflex has not been studied in man, although thoracic operations with lung perfusion and cardiac bypass might provide suitable conditions. Mills has shown that rapid intravenous infusions in men
cause hyperpnea, but the effect could originate from either the pulmonary vascular bed or the right side of the heart.

Multiple pulmonary embolism has been studied more frequently. Small emboli, 5 to 100 microns in diameter, cause rapid shallow breathing, sometimes after a short apnea, and these responses occur if only 3 to 10 per cent of the pulmonary circulation is blocked by the emboli, and if there is no immediate rise in pulmonary arterial pressure. Hyperventilation (judged by CO₂ tension measurements) occurs in animals in animals and in man. In animals the primary respiratory effects are usually prevented by vagotomy. Painful has suggested that the deflation receptors may be responsible.

The respiratory changes in embolism are complicated by considerable alterations in the pulmonary vascular bed, in lung mechanics and in the cardiovascular system. Blood pressure and heart rate fall, and there is pulmonary vasoconstriction with an increase in pulmonary arterial pressure; pulmonary edema may result. Lung compliance falls and total lung resistance to flow increases. There is a bronchial or bronchiolar constriction, which can be prevented by isoproterenol, but not by vagotomy. The extensive and sometimes contradictory literature on these responses points to vagal, sympathetic and possibly local reflexes, and also perhaps to direct chemical actions in the lungs; each of the motor effects will, in its turn, modify breathing, it is impossible at this stage to unravel the mechanisms of the respiratory changes in embolism. One clue should be considered: many, but not all, of the respiratory, cardiovascular and bronchomotor results of embolism are mimicked by injections of 5-hydroxytryptamine, which could be liberated during the formation of thrombi round the emboli.

Reflexes from the Respiratory Muscles, Joints and Tendons

This subject is considered because, although current knowledge of it is fragmentary and regrettably confusing, it is potentially of importance in physiology and in relation to inhalational therapy. There is no doubt that respiratory reflexes arise from the chest wall and diaphragm. The respiratory muscles contain spindle endings, and the diaphragmatic tendon has Golgi organs, both in animals and man. Nerve impulses from these and possibly from joint receptors have been recorded as action potentials in afferent nerves. The problem is twofold; first, that results on the respiratory reflex effects of stimulating and deforming respiratory muscles are contradictory, and the test effect being described for man. This agrees with the results of electrical stimulation of the central end of the phrenic or intercostal nerves, which indicates that their main reflex discharge is excitatory to respiratory muscle contraction. It also agrees with the observations of Floch that imposing resistances to the movements of the respiratory apparatus potentiates the contractions in those muscles tending to overcome the resistance; however, these resistance reflexes have been ascribed to an artefact due to tissue momentum, and the results of analysis of their nervous pathways arouse uncertainty. Nevertheless, as described so far, the reflex pattern is consistent with skeletal muscle stretch reflexes elsewhere in the body, and such reflexes have been described for the diaphragm and intercostal muscles.

However, in contrast to the general physiology of stretch reflexes, section of the phrenic nerve indicates that its tonic afferent activity inhibits respiratory muscles, and deformation of the chest wall and diaphragm of vagotomized animals suggests that the thoracic wall reflexes act in the opposite direction to lung volume reflexes, i.e., collapse of the chest wall inhibits inspiratory and augments expiratory muscle contractions. Since there is a con-
flict of results of animal experiments in which vagotomy and other nerve sections can isolate and simplify the reflex pathways being studied, it is not surprising that the patterns and importance of the thoracic wall reflexes for man have not yet been established.

Conclusions

Any interference, either deliberate or unintentional, with the normal pattern of breathing in man will modify the activity in many respiratory reflexes, and thereby adjust the discharge of the respiratory areas of the brain and spinal cord, and will also change cardiovascular and bronchomotor parameters. Although the qualitative pattern of these adjustments can be concluded from experiments in man and by analogy with work on animals, the quantitative assessment of their importance has been scarcely attempted either with normal subjects or with patients with respiratory ailments.

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OXYGEN BREATHING

Oxygen breathing in normal subjects causes a small decrease in heart rate which is abolished by atropine and a comparable rate-dependent decrease in cardiac output. It also increases systemic resistance and blood pressure. The oxygen effect on cardiac output, heart rate and circulation time persists in the circulatory response of reactive hyperemia. The effects of hyperoxia on heart rate of normal subjects is progressive with increasing concentrations of inspired oxygen from 15 to 100 per cent. A far higher range of chemoreceptor activity is suggested than has been previously generally recognized. (Daly, W. J., and Bondurant, S.: Effects of Oxygen Breathing on Heart Rate, Blood Pressure, and Cardiac Index of Normal Men—Resting, with Reactive Hyperemia, and After Atropine, J. Clin. Invest. 41: 126 (Jan.) 1962.)

CEREBRAL OXYGEN

In polarographic experiments on anesthetized dogs and rats, a shift from breathing air to breathing oxygen at atmospheric pressure, and also at a high pressure (OHP) of five atmospheres, raised availability of oxygen to the brain to levels well maintained throughout the exposure (20 to 55 minutes). Decompression reversed these effects. Cerebral vasoconstriction which may have occurred in OHP was apparently insufficient to prevent pronounced elevation of cerebral oxygen or to protect against oxygen toxicity. Addition of carbon dioxide (0.8 to 1.7 per cent) to the OHP usually raised the oxygen availability. (Bean, J. W.: Cerebral Oxygen in Exposures to Oxygen at Atmospheric and Higher Pressure, and Influence of Carbon Dioxide, Amer. J. Physiol. 201: 1192 (Dec.) 1961.)