Structure and Function of the Tracheobronchial System

N. Edward Robinson, B. Vet. Med., PhD, MRCVS

The tracheobronchial tree delivers and distributes air within the lung. Normally it provides a low resistance to airflow. Airway smooth muscle, the mucociliary system, the bronchial circulation, and cough provide neurally mediated protection of the lung from environmental challenges. Disease involves an exaggerated response of these mechanisms so that the airways become obstructed, distribution of ventilation is abnormal, and hypoxemia develops. Author’s address: Dept. of Large Animal Clinical Sciences, G-321 Veterinary Medical Center, Michigan State University, East Lansing, MI 48824-1314. © 1997 AAEP.

1. Introduction
The tracheobronchial tree is a system of branching tubes that begins distal to the larynx and ends at the level of the respiratory bronchioles. These conducting airways deliver air to the alveolar ducts and alveoli where gas exchange occurs. Diseases of the tracheobronchial tree are common. Viral respiratory diseases in young horses damage the mucociliary system and have effects on mucus secretion and regulation of smooth muscle. In racing animals, airway inflammation is clinically associated with poor performance and probably is due to a combination of infection and environmental contaminants in stables. Severe airway obstruction in older animals is the result of repeated exposure to dusts and molds and other contaminants in both stables and pastures. In these older heaves-affected animals, alterations in mucus secretion and smooth muscle tension are clearly associated with airway inflammation. This paper describes the structure and function of the tracheobronchial tree as it relates to the pathogenesis, diagnosis, and treatment of tracheobronchial disease in the horse.

In order to obtain sufficient oxygen during racing, a horse moves large volumes of air per minute in and out of its lungs by means of the tracheobronchial tree. The tracheobronchial tree provides a frictional resistance that opposes airflow and must be overcome by the work of the respiratory muscles. In addition, the tracheobronchial tree forms the anatomic dead space that does not participate in gas exchange. Ideally, the horse needs a wide airway to provide a low resistance but this would result in an unacceptably large dead space. In its evolution, the horse has had to compromise between its needs for an open airway for ease of gas delivery and the needs for low dead space in order to have efficient gas exchange.

In addition to delivering air for gas exchange, the tracheobronchial tree protects the lung from inhaled irritants such as dusts and pollutant gases, from antigens, and from infectious agents. The defense
mechanisms of the airways include cough, the mucociliary system, phagocytes, smooth muscle, and the bronchial circulation. These mechanisms prevent penetration of inhaled materials deeper into the lung and assist in the neutralization and elimination of such materials. Defense mechanisms are invoked to varying degrees in diseases of the tracheobronchial tree, and much of what we recognize as disease is an overreaction of these defenses so that the air passages are obstructed by bronchospasm, mucus accumulation, and airway wall thickening. This airway obstruction causes difficult breathing, impairs gas exchange, and reduces the horse’s performance.

2. Functional Anatomy of the Airways

The equine tracheobronchial tree branches in a monopodial manner. In each region of lung corresponding to a lobe, there is one major bronchus, which divides multiple times. At each branch point the daughter airway is much smaller than its parent, which progresses almost directly to the periphery of the lung. This branching pattern may be important in the distribution of inhaled particles. For example, the inhalation of foreign particles into the main bronchus of the caudal lobe could direct such material to the caudal part of the lobe. This may explain in part why the lesions of exercise-induced pulmonary hemorrhage occur in the most caudal part of the lung.

Airways are lined by a mucous membrane, consisting of the epithelium and lamina propria, under which are varying amounts of smooth muscle and cartilage (Fig. 1). In the trachea and bronchi, the epithelium is pseudostratified and columnar and consists of secretory goblet cells, ciliated cells, and cells with microvilli that participate in fluid and electrolyte exchange. The epithelial cells provide the mechanisms for mucociliary clearance. Submucosal glands also contribute secretions to the mucus blanket of the large airways. In the bronchioles the epithelium is simple cuboidal. The secretory cell is the Clara cell, and there are no goblet cells. Beneath the epithelium of the airways, the lamina propria contains a variety of sensory and motor nerves and blood vessels. These vessels are a plexus of the bronchial circulation and provide nutrients to the airway wall, aid in heating and humidifying air, and participate in the inflammatory response in airway disease. Cartilage provides firm support to the wall of the airways greater than 1–2 mm in diameter. In the trachea, U-shaped cartilages form most of the airway wall, and smooth muscle simply bridges the space between the tips of the cartilage dorsally. In the bronchi, cartilage plates encircle most of the airway but gradually become thinner and disappear toward the periphery. Simultaneously, the smooth muscle progressively encircles the airway until, in airways less than 1 mm in diameter, there is no cartilage and smooth muscle completely surrounds the airway. The small airways that lack cartilage are kept patent by the pull of the surrounding alveolar septa that insert into their walls.

3. Resistance to Airflow

During breathing, the respiratory muscles work to stretch and enlarge the lung and to move air through the air passages. Air movement is opposed by the resistance of the airways, the magnitude of which is determined primarily by the internal diameter of the trachea, bronchi, and bronchioles. The trachea and mainstem bronchi have a large diameter and therefore a much lower resistance than individual bronchioles. However, the diameter of the airways does not decrease progressively at each division, especially in the bronchioles where the parent and the daughter bronchiole can have a similar diameter. Consequently, as air flows from the trachea to the thousands of bronchioles, it is moving through a system
with an increasing total cross-sectional area (Fig. 2). This has several important consequences: (1) The trachea and large bronchi constitute the largest fraction of the airway resistance, and obstructions to this region therefore result in severe respiratory distress. (2) The bronchioles provide very little resistance to flow and therefore bronchiar obstruction must be diffuse to cause respiratory distress in the resting animal. (3) Airflow velocity is high and flow is turbulent in the large airways. Consequently, most of the sounds heard with a stethoscope originate from the larger airways. (4) Airflow velocity is low and flow is laminar in bronchioles. Sounds are generated in these airways only when turbulence results from airway obstruction by mucus, and so on. Because the bronchioles are held open by the tethering action of the surrounding lung, bronchiolar diameter increases and decreases as the lung inflates and deflates, respectively. Turbulence is most likely to occur when the bronchioles are narrowest. For this reason, wheezes originating in the bronchioles are best heard at the end of exhalation.

The effort being exerted by the respiratory muscles against the resistance of the airways is evaluated by measuring the change in pleural pressure during breathing \( \Delta P_{pl} \). This is most conveniently done by using an esophageal balloon.\(^1,2\) In the resting horse with healthy lungs, \( \Delta P_{pl} \) is up to 10 cm H\(_2\)O during a tidal breath. During exercise, \( \Delta P_{pl} \) is greater because larger volumes of air are being moved through the airways in less time. When the airways are narrowed by disease, \( \Delta P_{pl} \) must increase because airway resistance is high (Fig. 3). In general, an increase in \( \Delta P_{pl} \) parallels the clinical severity of airway obstruction in horses with heaves.

In addition to \( \Delta P_{pl} \), other measures of airway function include airway resistance \( (R_L) \) and dynamic compliance \( (C_{dyn}) \). Airway resistance reflects especially the function of the larger airways, whereas \( C_{dyn} \), or its inverse, dynamic elastance, is more indicative of peripheral airway diameter. An increase in \( R_L \) and a decrease in \( C_{dyn} \) are primarily a result of airway narrowing, which can be a result of bronchospasm, mucus obstruction, or airway wall thickening. In many obstructive diseases, these factors coexist and have important interactions with one another. Various indices from flow-volume loops have also been used to evaluate airway obstruction. Changes in flow-volume loops reflect changes in breathing strategy that are necessary to maintain gas exchange in the face of airway obstruction.\(^3\)

4. Regulation of Airway Smooth Muscle Contraction

The main regulator of airway diameter throughout the tracheobronchial tree is airway smooth muscle. In the healthy animal, smooth muscle is regulated primarily by the autonomic nervous system and by some interactions with the epithelium. In disease, airway narrowing results from the release of chemical mediators that cause smooth muscle contraction both directly and by interactions with nerves.

A. Neural Regulation of Airway Smooth Muscle

The classical descriptions of pulmonary innervation include two efferent (motor) systems (sympathetic and parasympathetic) and an afferent (sensory) system. Neural control of airway function is more complex than previously thought.\(^4\) In particular, the importance of nonadrenergic–noncholinergic (NANC) nerves has become obvious in recent years.\(^4-6\) A recent review includes an extensive description of the innervation of the equine lung.\(^7\)

A schematic diagram of the nerves that regulate airway smooth muscle contraction is shown in Fig. 4. The primary excitatory innervation in the trachea, bronchi, and bronchioles is provided by the parasympathetic system, which reaches the lung in the

![Fig. 2](image1.png) Diagram of the cross-sectional area of the tracheobronchial tree. Because this total area increases from the trachea to the bronchioles and alveoli, airflow velocity slows. Consequently, airflow changes from laminar in the larger airways to turbulent in the bronchioles.

![Fig. 3](image2.png) In the normal resting horse, inhalation requires a decrease in pleural pressure (\( \Delta P_{pl} \)) to approximately \(-10 \) cm H\(_2\)O. When the airways are obstructed a greater effort is required to move air, and this is reflected in a lower pleural pressure.
vagus. Activation of this system releases acetylcholine, which binds to M3-muscarinic receptors on airway smooth muscle. This in turn causes smooth muscle contraction and bronchospasm. There is no tonic parasympathetic activity in the horse; blockade of muscarinic receptors by atropine does not cause bronchodilation in normal animals. The parasympathetic system is activated when sensory receptors in the airway mucosa are stimulated by inhaled irritants, such as dusts and pollutant gases, or by mediators of inflammation. A protective reflex is initiated that gives rise to bronchospasm and increases mucus secretion.

The release of acetylcholine from parasympathetic nerves is regulated by receptors on the nerve terminals. A prejunctional muscarinic receptor provides negative feedback that normally inhibits the release of acetylcholine. In experimental allergic airway disease, the function of this receptor is deficient so that increased release of acetylcholine contributes to bronchospasm. We have been unable to find a similar defect in prejunctional receptor function in horses with airway disease. An α2 adrenoceptor also inhibits acetylcholine release and is probably activated during exercise to prevent parasympathetically mediated smooth muscle contraction.

Unmyelinated sensory nerves containing neuropeptides such as substance P also occur along the airways, especially around blood vessels in the lamina propria. When these sensory nerves are activated by inhaled irritants or mediators of inflammation, protective reflexes are initiated but in addition, neuropeptides are released locally by means of an axon reflex. A local release of neuropeptides increases blood flow through the submucosal bronchial plexus, increases vascular permeability, stimulates mucus secretion, and causes neutrophil chemotaxis. By initiating these changes, neuropeptides, such as substance P, calcitonin gene-related peptide, and neurokinin A, facilitate the inflammatory response and contribute to airway obstruction. These nerves form the excitatory nonadrenergic-noncholinergic (eNANC) system.

The inhibitory innervation of the airway smooth muscle is provided by the sympathetic and inhibitory nonadrenergic-noncholinergic (iNANC) systems. Even though sympathetic nerves occur throughout the airways, the norepinephrine that they release has little direct effect on smooth muscle except in the cranial trachea. It is important to realize, however, that even though they are not activated by norepinephrine released from sympathetic nerves, β2 adrenoceptors are present on smooth muscle throughout the airways. Activation of these receptors by circulating epinephrine or therapeutically by specific β2 agonists, such as clenbuterol, leads to smooth muscle relaxation. The iNANC system is the primary inhibitory system to horse airway smooth muscle. It provides inhibitory innervation to the smooth muscle of the trachea and large bronchi. Neurotransmission in the iNANC system involves nitric oxide and also may involve vasoactive intestinal peptide. The physiological role of the iNANC system is not well understood. In vitro studies have revealed an absence of iNANC inhibition in airways from heaves-affected animals.

B. Epithelial Factors

The epithelium produces factors that inhibit smooth muscle contraction. Although the epithelium is a source of inhibitory prostanoids such as prostaglandin E3 (PGE3), the epithelium-derived inhibitory factor appears not to be a prostanoid. Discovery of epithelium-derived inhibitory factors led to speculation that epithelial damage could lead to enhanced smooth muscle contraction. However, in the horse with chronic obstructive pulmonary disease, there appears to be more rather than less epithelium-derived inhibition of smooth muscle contraction.

C. Mediators of Inflammation

Several inflammatory mediators can cause bronchospasm. Histamine, the preformed mediator that is released from mast cells, causes bronchospasm by two mechanisms. By binding to histamine H1 receptors, it directly contracts equine airway smooth muscle. In addition, concentrations of histamine that cause only a small contraction dramatically augment the response of smooth muscle to activation of parasympathetic nerves. Serotonin has similar direct and indirect effects. Eicosanoids are metabolites of arachidonic acid, which is released from cell membranes in response to
many types of stimuli. The cyclo-oxygenase metabolites of arachidonic acid, the prostanoids (PG), have varied effects, depending on which prostanoid is produced and the receptor to which it is coupled. In the normal airways, PGE_2 is the primary cyclo-oxygenase product being produced, especially in the epithelium. PGE_2 inhibits smooth muscle contraction. In airway disease in other species, the bronchoconstrictor prostanoid PGD_2 is produced in increased amounts. Leukotrienes, products of the 5-lipoxygenase metabolism of arachidonic acid, have a variety of actions in airways such as neutrophil chemotaxis, increased mucus secretion, and bronchoconstriction. In the horse, aerosol administration of LTB_4 causes neutrophil accumulation in the lung, whereas the cysteiny leukotrienes (LTC_4, LTD_4, and LTE_4) cause airway smooth muscle contraction and respiratory distress. The effects of leukotrienes on airway smooth muscle are most consistent in the peripheral airways.

5. Mucociliary System
The tracheobronchial tree is lined by a layer of mucus-containing liquid that is transported toward the larynx by the action of cilia. Although the function of this mucociliary apparatus is altered by many diseases, there have been few specific studies of this system in horses. Wanner et al. compiled an excellent review of mucociliary clearance in health and disease.

The mucociliary system comprises a periciliary layer of fluid of low viscosity in which cilia beat. This is overlain by rafts or sheets of mucus in which foreign material becomes entrapped. These fluid layers originate in the goblet cells and submucosal glands from serous and mucous secretory cells. Beating of cilia is due to the interactions between microtubules within the cilium and includes an effective stroke, rest, and recovery stroke. During the effective stroke, the cilium is extended so that the claws at its tip engage the mucus rafts that float on the periciliary fluid. In recovery, the cilium is bent and moves caudally within the periciliary fluid. Several factors are important in maintaining normal mucociliary clearance. If the periciliary fluid depth is not sufficient, the cilium becomes entangled in the mucus and is sometimes called "mucociliary clearance.

Mucociliary clearance rates in horses have been measured by use of scintigraphy. Clearance is delayed when the horse's head is elevated by crossing and is increased when the head is lowered. Clearance is also delayed by the administration of xylazine or detomidine. Viral respiratory infections, especially equine influenza, also slow clearance rates. In the case of influenza, clearance rates do not return to normal for up to 1 month. These factors that depress mucociliary clearance are likely to make horses more susceptible to bacterial infections.

A. Ciliary Beating
The cilia on the surface of airway epithelial cells beat spontaneously and continuously, but their rate of beating changes in response to agonists that change the intracellular concentrations of cAMP and Ca^2+. Administration of β_2-adrenergic agonists increases cAMP and increases the rate of ciliary beating. Increases in intracellular Ca^2+ also increase beat frequency and occur in response to deformation of the epithelial surface and to cholinergic agonists such as acetylcholine. The net effect of inflammation is most likely a reduction in ciliary beat frequency. Leukotrienes and some prostanoids increase beat frequency; other substances, including the platelet-activating factor, hydrogen peroxide, eosinophil major basic protein, neutrophil elastase, neutral protease, and complements C3a and C5, decrease the rate of beating.

B. Mucus Secretion
Mucus is secreted from goblet cells and submucosal glands (Fig. 5). Secretion is increased by cholinergic, α- and β-adrenergic, and peptidergic neurotransmitters. Autonomic reflexes originating in tracheal and bronchial submucosal irritant receptors and C fibers promote mucus secretion. Long-term stimulation of secretion leads to an increase in the number of goblet cells and the size of submucosal glands.

Mucus is secreted in a condensed form and then becomes hydrated into a tangled polymer gel. The properties of this gel determine the viscosity of the mucus. Cholinergic stimulation makes mucus less transportable, whereas adrenergic stimuli have no effect. High viscosity (low transportability) is associated with low water content, high serum protein content (inflammation), and high DNA content (purulence).

Allergen challenge promotes mucus hypersecretion and increases the transport of fluid and electrolytes across the epithelium toward the airway lumen. Most inflammatory cell products increase mucus secretion. Leukotriene C_4 and leukocyte products, such as neutrophil elastase, promote mucus secretion; histamine causes water transport toward the airway lumen; and reactive oxygen species increase glycoconjugate release.

C. Mucociliary Function in Disease
Viruses that damage the tracheobronchial epithelium, e.g., influenza, decrease mucociliary clearance dramatically, presumably because of epithelial injury and shedding. Recovery takes several weeks. Bacterial and leukocyte products disrupt mucocili-
ary clearance by increasing mucus secretion and decreasing ciliary function. Some bacteria must attach to cilia to impair clearance, whereas others, notably *Pseudomonas aeruginosa*, produce soluble products that can impair ciliary beating and increase mucus secretion.

Anesthesia disrupts mucociliary function in part because the cuff of the endotracheal tube damages the epithelium. Clearance is also disrupted downstream from the cuff but the degree of impairment depends on the type of surgery. In humans, abdominal surgery is more deleterious to clearance than is orthopedic surgery.

6. Bronchial Blood Flow
The bronchial circulation, a branch of the systemic circulation, provides nutrient blood flow to the walls of the airways down to at least 1 mm in diameter. Bronchial vessels (V’s) are prominent in the lamina propria. Mucus is clearly visible in goblet cells (G’s) and is being extruded onto the surface (SMuc).

7. Cough
Cough is a mechanism to clear foreign material from the intrapulmonary airways. Cough is initiated by stimulation of irritant receptors located within and just below the epithelium. These receptors are most numerous in the lower trachea and in the large bronchi, i.e., in the airways that are most effectively cleared by coughing. When irritant receptors are activated, the following sequence of events occurs. After inhalation, the glottis closes and the expiratory muscles, especially the abdominal muscles, contract. This raises the pressure within the thorax and compresses the air within the lung. The glottis then opens and the compressed air is expelled at high velocity through the tracheobronchial tree. The clearance of large airways is facilitated because the high intrapleural pressure compresses these airways and reduces their cross-sectional area. As a result, flow velocity in the compressed airways is very high and this serves to blast out foreign material.

Cough is initiated when the irritant receptors are deformed by the presence of material on the epithelial surface. This can be foreign bodies or accumulated secretions. Deformation of cough receptors also occurs when smooth muscle contracts. For this reason, cough can be a sign of bronchospasm and is sometimes relieved by use of bronchodilator drugs. Airway disease results in cough for several reasons: mucociliary clearance frequently is impaired so that mucus accumulates in the airways, the sensitivity of irritant receptors is increased by inflammation, and epithelial desquamation exposes irritant receptors more directly to the airway lumen. The latter occurs in the presence of viral respiratory diseases, and recovery of the normal epithelial surface may take up to 5 weeks.

8. Airway Wall Thickness
Structural changes within the airway wall, which result in airway wall thickening, may play an important role in airway obstruction. Moderate amounts of airway wall thickening, which have little effect on baseline caliber, can markedly accentuate the effects of smooth muscle shortening on the degree of airway narrowing. These effects are greater when the airway wall thickening is localized to the peripheral rather than the central airways. Recently, Broadstone et al. demonstrated thickening of the airway wall in horses with chronic obstructive pulmonary disease.

9. Consequences of Airway Obstruction
As stated above, obstructions of the large airways cause severe respiratory distress because these air passages form the narrowest point in the tracheobronchial system. Foreign bodies would provide
such an obstruction. In most chronic airway diseases, inflammation is most intense in the bronchi-oles, which are obstructed by a mixture of broncho-spasm, mucus plugging, and airway wall thickening. If the obstruction is diffuse and severe, airway resistance may be sufficiently increased to result in signs of respiratory distress in the resting animal. Such is the case in the horse with severe heaves. More commonly, obstruction is less severe so that there are no signs of respiratory distress in the resting animal. However, animals with low-grade bronchiolitis (small airway disease) may not perform adequately. This is because the small airway ob-struction results in uneven distribution of ventil-ation within the lung.

The distribution of ventilation is one of the main factors determining the gas-exchange efficiency of the lung. Uneven ventilation distribution leads to ventilation-perfusion mismatching, which results in hypoxemia. When small airways are obstructed, ventilation distribution becomes more uneven as respiratory rate increases. Exercise requires an increase in respiratory rate, and therefore small airway disease most likely leads to uneven ventila-tion distribution during exercise. It is highly likely that it is this uneven distribution of ventilation that is the cause of poor performance in horses with low-grade inflammatory airway disease.

This research was supported by grants from 3M Animal Care Products and Bayer AG.

References and Footnotes


