ADVANCES IN VETERINARY SCIENCE AND COMPARATIVE MEDICINE

Edited by

CHARLES E. CORNELIUS   CHARLES F. SIMPSON

Volume 26

THE RESPIRATORY SYSTEM

ADVANCES IN VETERINARY SCIENCE AND COMPARATIVE MEDICINE

Edited by

CHARLES E. CORNELIUS
California Primate Research Center
University of California
Davis, California

CHARLES F. SIMPSON
Department of Preventive Medicine
College of Veterinary Medicine
University of Florida
Gainesville, Florida

Volume 26

THE RESPIRATORY SYSTEM

Guest Editor

D. L. DUNGWORTH
Department of Veterinary Pathology
School of Veterinary Medicine
University of California
Davis, California

1982

ACADEMIC PRESS
A Subsidiary of Harcourt Brace Jovanovich, Publishers
New York London
Paris San Diego San Francisco São Paulo Sydney Tokyo Toronto

ACADEMIC PRESS, INC.
111 Fifth Avenue, New York, New York 10003

United Kingdom Edition published by
ACADEMIC PRESS, INC. (LONDON) LTD.
24/28 Oval Road, London NW1 7DX

LIBRARY OF CONGRESS CATALOG CARD NUMBER: 53-7098

ISBN 0-12-039226-7

PRINTED IN THE UNITED STATES OF AMERICA

82 83 84 85 9 8 7 6 5 4 3 2 1

CONTRIBUTORS

Numbers in parentheses indicate the pages on which the authors' contributions begin.

R. G. BREEZE, Department of Microbiology and Pathology, Washington State University, Pullman, Washington 99164 (201)

J. R. CARLSON, Department of Animal Sciences, Washington State University, Pullman, Washington 99164 (201)

D. L. DUNGWORTH, Department of Veterinary Pathology, School of Veterinary Medicine, University of California, Davis, California 95616 (173)

R. N. GOURLAY, Agricultural Research Council, Institute for Research on Animal Diseases, Compton, Newbury, Berkshire, England (289)

F. F. HAHN, Lovelace Biomedical and Environmental Research Institute, Albuquerque, New Mexico 87185 (35)

C. J. HOWARD, Agricultural Research Council, Institute for Research on Animal Diseases, Compton, Newbury, Berkshire, England (289)

GEORGE J. JAKAB, Department of Environmental Health Sciences, The Johns Hopkins School of Hygiene and Public Health, Baltimore, Maryland 21205 (155)

J. L. MAUDERLY, Lovelace Biomedical and Environmental Research Institute, Albuquerque, New Mexico 87185 (35)

K. PERK, The Hebrew University of Jerusalem, Rehovot Campus, Rehovot 76 100, Israel (267)

N. E. ROBINSON, Departments of Physiology and Large Animal Surgery and Medicine, Michigan State University, East Lansing, Michigan 48824 (1)

JAMES W. RYAN, Department of Medicine, University of Miami School of Medicine, Miami, Florida 33101 (79)

UNA S. RYAN, Department of Medicine, University of Miami School of Medicine, Miami, Florida 33101 (79)

DAVID O. SLAUSON, Department of Pathology, College of Veterinary Medicine, Cornell University, Ithaca, New York 14853 (99)

B. N. WILKIE, Department of Veterinary Microbiology and Immunology, Ontario Veterinary College, University of Guelph, Guelph, Ontario, N1G 2W1 Canada (233)

PREFACE

This volume of *Advances in Veterinary Science and Comparative Medicine* is devoted to the respiratory system. Relatively more progress has been made in the last decade toward the understanding of the biology and diseases of the lung than for most other major organs. From the large amount of available material, topics were chosen because they represent areas where major developments can be expected to lay the groundwork for important advances in recognition and prevention or treatment of a variety of pulmonary diseases. The contributions on selected aspects of pulmonary function, pulmonary inflammation and defense, and chemical, allergic, and infectious injury will be of interest to those concerned with diseases in animals or man.

Three articles relate to pulmonary function. The first, on functional consequences of species differences in lung anatomy, focuses on variations in amount of collateral ventilation and their influence on pulmonary vascular responses to hypoxia and on structural patterns of pulmonary disease. The second summarizes available data on changes in conventional lung function observed in aging animals as compared to man. The subject is pertinent to those involved in clinical evaluations of pulmonary function in old animals and those studying "models" of aging. The third article covers metabolic functions of pulmonary vascular endothelium. This is one of the most exciting fields of pulmonary research. Recognition that pulmonary endothelium participates actively in a wide variety of metabolic activities has tremendous implications for the role of the lung in preserving bodily homeostasis and for the development of therapeutic approaches to a variety of disorders involving the lung.

Three articles deal with aspects of pulmonary inflammation and manifestation of disease. One reviews information regarding mediators of the pulmonary inflammatory response. Such information forms a necessary base for the understanding of pulmonary disease and will help lead to more effective therapeutic intervention. A second article addresses the role of viral–bacterial interactions in the pathogenesis of bacterial pneumonias. In view of the importance of bacterial pneumonias in animals, particularly under systems of intensive management, this is an area of crucial concern. A third article outlines general features and causes of the broad category of interstitial pulmonary disease. The interstitial pneumonias are being recognized with increasing frequency and often present difficult clinical problems.

There are four contributions on various etiologic categories of pulmonary disease. One on chemical-induced lung injury sheds important light on toxic conditions in cattle and horses. The knowledge gained about the pathogenesis of acute bovine pulmonary emphysema and edema is particularly striking. A second contribution on allergic respiratory disease in animals describes the variety of conditions where an allergic mechanism is suspected but less often proved. A third compares and contrasts two important slow virus infections of sheep, *maedi* and pulmonary adenomatosis, and presents recent evidence confirming that pulmonary adenomatosis is also caused by a retrovirus. A fourth article reviews current knowledge concerning the important role played by mycoplasmas in causing respiratory disease in a variety of animals.

The sterling efforts of my coauthors, the able assistance of the staff of Academic Press, and the encouragement of C. E. Cornelius and C. F. Simpson are gratefully acknowledged.

D. L. DUNGWORTH

CONTENTS

Some Functional Consequences of Species Differences in Lung Anatomy

N. E. ROBINSON

The Effects of Age on Lung Function and Structure of Adult Animals

J. L. MAUDERLY AND F. F. HAHN

Metabolic Functions of the Pulmonary Vascular Endothelium

JAMES W. RYAN AND UNA S. RYAN

The Mediation of Pulmonary Inflammatory Injury

DAVID O. SLAUSON

Viral–Bacterial Interactions in Pulmonary Infection

GEORGE J. JAKAB

Interstitial Pulmonary Disease

D. L. DUNGWORTH

Chemical-Induced Lung Injury in Domestic Animals

R. G. BREEZE AND J. R. CARLSON

Allergic Respiratory Disease

B. N. WILKIE

Slow Virus Infections of Ovine Lung

K. PERK

Respiratory Mycoplasmosis

R. N. GOURLAY AND C. J. HOWARD

Some Functional Consequences of Species Differences in Lung Anatomy

N. E. ROBINSON

Departments of Physiology and Large Animal Surgery and Medicine, Michigan State University, East Lansing, Michigan

ISBN 0-12-039226-7

I. Introduction

The lung's major function, gas exchange, is accomplished by the apposition of air and blood in the peripheral gas exchange portions of the lung. The delivery of air is determined by the effort exerted by the respiratory muscles, the elasticity of the lung and chest wall, and the flow resistance of the airways, while the delivery of blood is determined by the driving pressure in the pulmonary circulation and flow resistance in the vascular bed. Ideally, each terminal gas exchange unit receives air and blood in a ratio of 0.8–1.0 resulting in optimal gas exchange. Even in healthy lungs, however, ventilation and blood flow are not uniformly distributed, and in the animal with lung disease this maldistribution is accentuated so that some regions are relatively overventilated while others are relatively overperfused (Wagner *et al.*, 1975). The net result of this mismatching of ventilation and blood flow is impaired gas exchange.

Mechanisms suggested to facilitate the matching of ventilation and blood flow include collateral ventilation between adjacent regions of lung (Van Allen *et al.*, 1931), hypoxic vasoconstriction in pulmonary vessels (Euler and Liljestrand, 1947), and hypocapnic bronchoconstriction (Nisell, 1950). The aim of this article is to review the extent to which these mechanisms interact to maintain gas exchange in disease and to describe how the species differences in lung anatomy might affect the relative importance of these mechanisms. The discussion is largely limited to the species of common veterinary concern, namely, cattle, sheep, pigs, horses, dogs, and cats.

II. Anatomy

Lungs can be classified by the degree of lobation and lobulation, by the anatomy of the tracheobronchial tree, and on the basis of subgross anatomy defined by McLaughlin *et al.* (1966) as the "finer structures whose morphologic characteristics and relationships are best revealed through the use of the dissecting microscope and injection techniques."

A. Lobation

Hare (1955) defines a lobe as "a large area of pulmonary tissue which is ventilated by a large bronchus arising either from a main bronchus or from the trachea; it is separated from neighboring lobes by interlobar fissures which may be continued by connective tissue planes." Using this definition, the right lung of dogs, cats, cattle, sheep, and pigs is composed of four lobes: an anterior (cranial or apical), a middle (or cardiac), a posterior (caudal or diaphragmatic), and an accessory (or mediastinal). The left lung of these species is composed of two lobes, an anterior (cranial or apical) and a posterior (caudal or diaphragmatic). The left anterior lobe is deeply divided by a fissure into an apical and a cardiac segment. These segments do not anatomically constitute lobes because their bronchi do not arise directly from a mainstem bronchus. However, they may function like lobes because they are surrounded almost completely by visceral pleura. Ruminants differ from other species in that the right anterior lobe bronchus arises from the trachea rather than from the mainstem bronchus (Stamp, 1948; Hare, 1955; Suzuki and Ohkubo, 1977). Although the horse lung is not obviously divided by fissures into lobes, Hare (1975) and Suzuki and Ohkubo (1977) describe an apical, diaphragmatic, and accessory lobe in the right lung and an apical and diaphragmatic lobe in the left lung. It is not known if the horse lung is divided by complete connective tissue septa into regions equivalent to the cranial and caudal lobes of other species. The accessory lobe can be dissected away from the remainder of the lung along fascial planes (Robinson and Sorenson, 1978).

In human pulmonary anatomy, portions of a lobe supplied by each major subdivision of a lobar bronchus are known as bronchopulmonary segments. Various authors have described the bronchopulmonary segments of sheep (Hare, 1955), cattle (Stamp, 1948), goat (Nanda and Patel, 1968), buffalo (Nanda and Malik, 1968), and cat (Adrian, 1964) lungs, allowing prediction of the regions of lung affected by obstructions of major divisions of the bronchial tree.

B. Subgross Anatomy

McLaughlin *et al.* (1961) divided mammalian lungs into three types based on the subgross anatomy of the secondary lobules, pleura, and peripheral airways and on bronchovascular relationships and bronchial arterial distribution. Cattle, sheep, and pig lungs (group I) have extremely well developed lobulation with secondary lobules distinctly separated by fascial planes. The secondary lobule is defined as the smallest discrete portion of lung which is surrounded by connective tissue septa. It is irregularly polyhedral and is estimated to contain from 30 to 50 primary lobules. The pleura of group I mammals is thick and supplied by the bronchial artery. Distal airways are primarily terminal bronchioles with few respiratory bronchioles. The bronchial artery terminates at the distal airways, and the pulmonary veins follow the bronchi and pulmonary arteries to the periphery of the lung.

Dog, cat, and monkey lungs (group II) are not subdivided into secondary lobules. The pleura are thin and supplied by the pulmonary artery. Terminal bronchioles are absent, but respiratory bronchioles are well developed. The bronchial artery terminates in distal airways. The pulmonary veins course through the lung parenchyma at some distance from the bronchi and pulmonary arteries.

Horse lungs (group III) like group I lungs have a thick pleura supplied by the bronchial artery and poorly developed respiratory bronchioles. Connective tissue septa between secondary lobules are incomplete. The bronchial artery terminates in the distal airways and alveoli. The pulmonary vein follows the bronchus and artery in the periphery but departs from these structures as it approaches the hilum.

In addition to the distribution of the pulmonary vein described above, the pulmonary vasculature of various species differs in the thickness of the muscular layer. In calves and pigs, pulmonary arteries (and veins) have a thick muscle layer. In dogs and cats the muscle layer is thin (Tucker *et al.*, 1975).

McLaughlin *et al.* (1961) point out that the functional consequences of species differences in subgross anatomy are unknown but speculate on differences in collateral air drift between secondary lobules. Although there have been studies of the functional consequences of lung injury utilizing a variety of different species since McLaughlin *et al.* (1961) described species differences in subgross anatomy, investigators have not interpreted their data in light of these differences except in relation to collateral airflow. A large part of this article is therefore concerned with how differences in lobation and lobulation affect the flow of air between adjacent regions of lung and how this determines the effects of airway obstruction in different species.

III. Collateral Ventilation and Interdependence

The transfer of air between adjacent lobules was first demonstrated in dogs by Van Allen and co-workers (1930). When a cannula was tied in the lumen of a segmental bronchus and air blown down the cannula, not only did the lobules subtended by the cannula inflate, but air also escaped from the mainstem bronchus, indicating passage of air between the "isolated" segment of lung distal to the wedged cannula and the remainder of the lung. In subsequent studies, Van Allen and coworkers (1931) demonstrated the lack of collateral airflow in the completely lobulated pig and calf lungs and the ease of collateral airflow in nonlobulated dog and cat lungs. By obstructing a dog bronchus with a cannula, the end of which was under water and ventilating the remainder of the lung, they demonstrated that air always escaped from the cannula during exhalation. Presumably air entered the lung segment distal to the obstruction through collateral pathways during inhalation. Van Allen and co-workers (1931) termed the collateral transfer of air between lobules "collateral respiration." The term "collateral ventilation" has now replaced collateral respiration.

A. Pathways for Collateral Ventilation

The three pathways proposed for collateral ventilation are (1) interalveolar pores of Kohn, (2) the bronchiole alveolar communications described by Lambert (1955), and (3) anastomosing respiratory bronchioles and alveolar ducts described by Martin (1966).

Interalveolar pores which have a diameter of 3–13 μm (Macklin, 1935) increase in number with age in dogs (Martin, 1963). Because it is possible to pass microspheres up to 120 μm in diameter between adjacent segments of dog lung (Martin, 1966), and because pores provide a very high resistance to airflow (Sasaki *et al.*, 1980), it is unlikely they are the major pathway for collateral ventilation.

The second proposed pathway is the accessory bronchiole alveolar communication which has a diameter up to 30 μm and connects distal bronchioles with surrounding alveoli (Lambert, 1955). These communications have been described in humans, cats, rabbits, and sheep (Krahl, 1959).

Because Martin (1966) could pass 120-μm microspheres between adjacent lung segments of dogs, he attempted to identify collateral pathways with an aerosol of India ink. He observed staining of respiratory bronchioles rather than alveolar pores and by serial sectioning demonstrated respiratory bronchioles and alveolar ducts anastomosing between adjacent lung segments. He concluded that collateral ventilation occurs through respiratory bronchioles rather than through interalveolar pores of Kohn. More recently, Raskin and Herman (1975) have also described 200-μm interacinar pathways between respiratory bronchioles and alveolar ducts in human lungs. Interacinar pathways and anastomosing respiratory bronchioles have not been reported in other species. In their response to vagal stimulation (Olson and Robinson, 1980), to carbon dioxide (Traystman *et al.*, 1976), and to changes in lung volume (Woolcock and Macklem, 1971; Menkes *et al.*, 1973), collateral pathways behave like peripheral airways.

B. Measurement Techniques in Collateral Ventilation

Physiological properties of collateral airways are investigated by timed collections of expired air from a collaterally ventilating lung region (Van Allen *et al.*, 1931) by measurement of the resistance to airflow across collateral pathways (Hilpert, 1970) and by measurement of the time constant for collateral ventilation (Hilpert, 1970; Woolcock and Macklem, 1971).

Data obtained by timed collections of expired gas from a collaterally ventilating region of lung are difficult to interpret because air that enters the region via collaterals during inhalation can leave either via the wedged bronchial catheter or via collateral airways during exhalation (Lindskog and Bradshaw, 1934).

1. Collateral Airway Resistance

Collateral airway resistance is measured by wedging a double lumen catheter in a peripheral airway (usually a 5-mm-diameter bronchus) and isolating a subsegmental region of lobe. Gas is blown down the outer lumen of the catheter at a known flow rate and leaves the isolated region of lung via collateral pathways. The driving pressure for collateral flow is measured between the tip of the double lumen catheter and the trachea. Resistance calculated from the driving pressure gradient and gas flow includes the resistance of airways within the isolated segment of lung between the wedged catheter and the collateral pathways, the resistance of collateral pathways, and the resistance of extrasegmental airways between the collaterals and the trachea. Because collateral gas flows are small and the cross-sectional area of extrasegmental airways is great, the resistance of these latter airways is considered negligible. However, the resistance of peripheral airways within the isolated segment comprises a significant portion of the measured resistance (Robinson and Mukhtar, 1977; Sasaki *et al.*, 1980), and it is therefore impossible to state with certainty if a given intervention which alters collateral resistance is affecting intrasegmental airways or collateral pathways.

2. Time Constant for Collateral Ventilation

The collateral time constant is the time for 63% pressure equilibration between an isolated segment and the remainder of the lung. It is measured from the pressure decay following arrest of airflow into an isolated region of lung (Hilpert, 1970) or from the phase lag between pressures in the lung and an isolated region of lung during sinusoidal