Exercise and Sports Pulmonology

Pathophysiological Adaptations and Rehabilitation

Annalisa Cogo
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Editors
Annalisa Cogo
Centre for Exercise and Sport Science
University of Ferrara
Ferrara
Italy

Matteo Bonini
National Heart and Lung Institute
Imperial College London
London
UK

Paolo Onorati
Internal medicine Department,
Ospedale Civile di Alghero
ASSL Sassari, ATS Sardegna
Alghero
Italy

ISBN 978-3-030-05257-7 ISBN 978-3-030-05258-4 (eBook)
https://doi.org/10.1007/978-3-030-05258-4

Library of Congress Control Number: 2019930437

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Foreword

Exercise is arguably the cardinal stressor to the lungs, whether in the elite athlete or the highly compromised patient with chronic respiratory disease. This is the ambitious theme of *Exercise and Sports Pulmonology: Pathophysiological Adaptations and Rehabilitation*, for which one should perhaps be mindful of Joseph Barcroft's (1872–1947) aphorism that "The condition of exercise is not a mere variant of the condition of rest, it is the essence of the machine" (*Features in the Architecture of Physiological Function*. Cambridge University Press, p 286, 1934). And while the "*machine*" itself is common to both athlete and patient, the systemic manifestations of its "*essence*" that ultimately lead to exercise intolerance naturally differ widely; as do the means at hand to extend their tolerable system limits for sporting accomplishment and for the maintenance of activities of daily living. The Editors—Annalisa Cogo, Matteo Bonini, and Paolo Onorati—have attracted a cadre of international investigators who insightfully address this broad continuum of human performance from a perspective of physiological and pathophysiological system integration for the athlete, the patient, the athlete as patient, and the patient as athlete.

Susan A. Ward
University of Leeds,
Leeds, UK

Preface

Lungs play a pivotal role in exercise, and respiratory impairment, due to both acute and chronic lung diseases, can have a significant impact on physical performance. Furthermore, recent evidence shows that exercise is an effective and safe intervention for prevention and rehabilitation in respiratory diseases. As pulmonologists interested in "lung and exercise" and as sports physicians focused on "exercise and lung," we perceived the lack of a text specifically dedicated to this topic. We therefore thought of a text that could gather worldwide experts in a broad variety of topics concerning the relationship between lung and exercise. When the Springer's invitation arrived to plan a text on sport and lung, we accepted immediately.

We started working on a text that included the adaptations of the respiratory system during exercise, the clinical and functional assessment of subjects affected by respiratory diseases, and the eligibility and limitations to the execution of sport activity in chronic respiratory diseases with particular attention to the diagnosis, prevention, and treatment of exercise-induced bronchoconstriction also in view of the World Anti-Doping Agency rules. We included also sections concerning respiratory muscle training and rehabilitation and a section dealing with the relationships between the environment and sports. This book provides an updated overview on the link between lungs and exercise, both in healthy active subjects and in those with chronic respiratory diseases. As the first comprehensive text on this topic, we do hope it could raise reader's interest and fill a relevant unmet need.

We thank Springer for the innovative project and for the trust conferred and all the authors for having adhered enthusiastically and with dedication to our proposal.

Ferrara, Italy — Annalisa Cogo
London, UK — Matteo Bonini
Alghero, Italy — Paolo Onorati

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Carli M. Peters and A. William Sheel

Abstract

The pulmonary system is a key element within the integrated network responsible for maintaining blood gas homeostasis. In all physiologic states, including rest, sleep, and dynamic exercise, its primary function is to ensure that mixed venous blood is transformed into arterial blood with appropriate partial pressures of O_2 and CO_2. This system faces several significant challenges to its ability to maintain blood gas homeostasis during dynamic exercise. With a simultaneous increase in mixed venous carbon dioxide content and decrease in mixed venous oxygen content, ventilatory demands are significantly greater during exercise than during rest. A reduction in transit time of red blood cells through the pulmonary capillaries, resulting from an increased cardiac output, also decreases the time available for gas exchange. To maintain blood gas homeostasis despite these challenges, medullary neural networks and sensory reflex mechanisms tightly regulate alveolar ventilation. The structural capacity for producing ventilation and increasing diffusion surface area to meet the demands of dynamic exercise in the healthy respiratory system is truly remarkable.

1.1 Introduction

The human respiratory system serves multiple functions. First, this system is responsible for maintaining blood gas homeostasis by precisely matching the level of ventilation to the metabolic requirement of oxygen delivery and carbon dioxide elimination. As a given level of ventilation can be achieved in several ways, the

C. M. Peters · A. W. Sheel (✉)
School of Kinesiology, The University of British Columbia, Vancouver, BC, Canada
e-mail: bill.sheel@ubc.ca

A. Cogo et al. (eds.), *Exercise and Sports Pulmonology*,
https://doi.org/10.1007/978-3-030-05258-4_1

respiratory system must fine-tune the breathing pattern so that maintenance of blood gases is achieved at a minimum energy cost. Second, by regulating the body's CO_2 stores, the lung maintains an appropriate acid-base balance. Lastly, the lung receives the entire cardiac output, and pulmonary vascular pressure and resistance must remain low to prevent increasing the load on the right heart or damaging the thin alveolar-capillary interface. At rest and during moderate-intensity exercise, the structural and functional capacities of the respiratory system generally exceed the demands placed on the system, and the aforementioned functions are readily achieved. However, significant pulmonary limitations to exercise performance and oxygen delivery may occur during high-intensity exercise. This chapter focuses on the structure and function of the healthy human respiratory system and how the increased ventilatory requirements of exercise are met.

1.2 The Structure of the Human Respiratory System

The lungs, airways, rib cage, and respiratory muscles comprise the respiratory system. The design of the human lung is such that it permits air and blood to be in close proximity over a very thin (about 0.3 μm in some places), large (approximately 50–100 m) surface area. Its primary function is gas exchange, to allow oxygen to move from inspired air into the blood and carbon dioxide to move out. Fick's law of diffusion states that the amount of gas that moves through a sheet is inversely proportional to the thickness and proportional to the area; therefore, the structure of the blood-gas barrier is ideally suited for gas exchange. The airways are a series of branching tubes that from proximal to distal decrease in radius and length and become more numerous. Though multiple models of the human airway tree have been proposed, the most widely accepted model is that of Weibel, which numbers successive airway generations from the trachea (generation 0) down to the alveoli (generation 23) [1]. A regular dichotomy, with each bronchus regularly dividing into two daughter bronchi of approximately equal size, is assumed with this model. Three-dimensional reconstruction of computed tomography scans has demonstrated that a regular dichotomy occurs until the sixth generation of airways, but trifurcations and airways that terminate early may occur beyond this point [2]. The lungs and airways are protected within the chest cavity by the rib cage. The rib cage consists of the sternum and 12 pairs of ribs anchored posteriorly to the 12 thoracic vertebrae. The respiratory muscles modify the volume of the chest wall to produce the pressures required for inspiratory and expiratory flow generation.

An appropriate level of ventilation is maintained by the coordinated contraction of upper airway muscles and the inspiratory and expiratory muscles. Due to the negative pleural pressure developed during inspiration, muscles of the upper airways are responsible for stiffening and dilating the upper airways to ensure they don't collapse. The primary muscle of inspiration is the diaphragm. When the diaphragm contracts, the abdominal contents are pushed downward and forward and the chest cavity increases in size. Other inspiratory muscles include the external intercostals, scalene muscles, and sternocleidomastoids. Upon contraction, the

external intercostals pull the ribs upward and forward, the scalene muscles elevate the first two ribs, and the sternocleidomastoid raises the sternum. The primary expiratory muscles are the abdominal muscles, including the rectus abdominis, internal and external oblique muscles, and the transverse abdominis. Intra-abdominal pressure increases upon contraction of these expiratory muscles and pushes the diaphragm upward. The internal intercostals pull the ribs downward and inward and assist with expiration.

1.3 Control of Breathing

Precise regulation of the respiratory pattern requires a control system that is capable of generating a respiratory rhythm, ensuring that the motor output to respiratory muscles is timed appropriately, and receiving sensory feedback from the periphery [3]. It is generally agreed upon that the generation of a respiratory rhythm is controlled by the central pattern generator that is made up of groups of neurons located in the pons and the medulla. Within the ventrolateral medulla, there is a group of cells known as the pre-Botzinger complex that appears essential for generating the respiratory pattern [4]. In the medulla, a group of cells referred to as the dorsal respiratory group is mainly associated with inspiration, and another group of cells, the ventral respiratory group, is associated with expiration. The respiratory rhythm is passed from these neurons to the phrenic, intercostal, and abdominal motor nerves via the spinal cord allowing the respiratory muscles to generate an appropriate pressure. To ensure proper timing of motor output to the respiratory muscles, premotor neurons are present in the medullary pattern generator that know what other neurons are doing throughout the breathing cycle [5].

1.3.1 Chemical and Mechanical Sensory Inputs

The respiratory pattern generator receives several types of feedback to fine-tune respiration. Humans have two types of chemoreceptors: one located in the medulla and bathed in brain interstitial fluid and the other located near the bifurcation of the carotid artery and exposed to arterial blood. A highly regulated ion composition is maintained in the cerebral fluid surrounding the medullary chemoreceptors due to the selective permeability of cerebral blood vessels. This selective permeability results in carbon dioxide easily entering the interstitial fluid and quickly changing the pH, whereas metabolic acids and bases in the plasma enter the brain interstitial fluid very slowly. Central chemoreceptors respond to changes in PCO_2, and though they don't respond as rapidly as peripheral receptors, after several minutes of increased PCO_2, the central chemoreceptors are responsible for most of the increase in ventilation. Peripheral chemoreceptors are small organs that respond rapidly to changes in pH, PCO_2, and PO_2 in blood on the way to the brain. These small organs receive the highest blood flow per gram of tissue of any organ in the body. The carotid sinus nerve relays sensory information from the carotid bodies to stimulate

the brainstem medullary respiratory neurons and shape motor nerve output to the respiratory muscles. The respiratory center also receives feedback on the mechanical state of the lung. The lung is innervated by vagal afferents that during inspiration and activation of pulmonary stretch receptors send feedback to the medulla via the vagus nerve (cranial nerve X) to inhibit inspiration. In response to low lung volumes, receptors in the lung can also provide excitatory input to the respiratory neurons. The diaphragm and abdominal muscles, similar to other skeletal muscles, also contain receptors classified as primarily mechanical (type III) and primarily metabolic (type IV) [6]. Contraction-induced mechanical and chemical stimuli activate these receptors and send feedback to the medulla via afferent fibers within the major motor nerves [7]. Feedback from these receptors plays a major role in controlling both ventilation and circulation during exercise.

1.4 Breathing Mechanics

Contraction of the inspiratory muscles reduces the pressure within the alveoli compared to atmospheric pressure and establishes the pressure gradient required to generate airflow into the lungs. Both the resistance to flow through the airways and the elastic recoil of the lung must be overcome by the inspiratory muscles during inspiration. Resistance to flow through the airways, governed by Poiseuille's law, is primarily dependent on airway radius. As lung volume is increased, tethering of the airways leads to a reduction in resistance to flow. The elastic recoil of the lung is such that without the outward recoil of the chest wall, the lung would collapse to its smallest volume. Elastic tissues such as collagen and elastin, as well as surface tension of the liquid film lining the alveoli, contribute to the lung's elastic behavior. At functional residual capacity (FRC), defined as the volume of air in the lung after a normal expiration, elastic recoil of the lung is balanced by the outward recoil of the chest wall. The elastic nature of the lung at any given volume is defined by compliance, the change in lung volume for a given pleural pressure change (Δvolume/Δpressure). The compliance of the lung is about 200 mL cm H_2O^{-1} within the range of inflation pressures generated during resting tidal breathing (between -5 and -10 cm H_2O) but is much stiffer and less compliant at high lung volumes. During dynamic exercise, the pressure, volume, and flow rate demands placed on the respiratory system are significantly increased, and precise regulation of the resistive and elastic behavior of the system is required to prevent excessive respiratory muscle work.

1.4.1 Control of Airway Caliber

The airways can be categorized as extra- or intrathoracic with the nasal, pharyngeal, and laryngeal airways considered to be the primary extrathoracic or "upper airways." For a detailed treatment of the anatomy and physiology of the upper airway, the reader is directed to Dempsey et al. [8]. The extrathoracic airways provide the majority of total respiratory system flow resistance. During strenuous exercise,

there is a significant negative intrathoracic pressure, and this downstream pressure renders the extrathoracic airways particularly susceptible to narrowing during inspiration. Fortunately, the change in airflow from a nasal route (high resistance) to an oral route (low resistance) that occurs at minute ventilations of approximately 20–40 L/min serves to reduce airway resistance. Activation of the upper airway musculature during inspiration provides a "stiffening" of the extrathoracic airways which provides "traction" to abduct and dilate the upper airways [9]. The mechanisms by which activation of the upper airway muscles modulate airway resistance are unclear. However, there is some indirect evidence that activation occurs via feedforward [10] and feedback mechanisms [11].

The intrathoracic airways are susceptible to narrowing via constriction of bronchial smooth muscle. However, in humans free from respiratory disease, it is known that intrathoracic resistance is lower during and following whole-body exercise [12]. Dilation of the bronchi with exercise occurs via a reduction in cholinergic tone to the airway smooth muscle [13, 14]. There is also a significant mechanical aspect to exercise-induced bronchodilation whereby lung stretch at a high tidal volume "tethers" the airways [15].

1.4.2 Flow-Volume Relationships

During resting breathing (or eupnea), the airways expand slightly on inspiration and during quiet expiration return to their normal diameter. Expiration is typically longer than inspiration, and the average flow rates are generally smaller during expiration. When expiration is forced, airway mechanics and associated flows differ substantially from inspiration. A maximal flow-volume curve for an individual can be generated by having the subject inspire until total lung capacity (TLC), expire as hard and fast as they can to residual volume (RV), and then immediately forcefully inspire back to TLC. The resulting flow-volume curve has a characteristic shape in healthy young subjects, which can be seen in Fig. 1.1. As lung volume falls during the forced expiration, flow rate also falls considerably. This differs from the forced inspiration where flow rate remains relatively constant and results in the average flow rate being greater during inspiration than expiration. Interestingly, the expiratory limb of the flow-volume curve is remarkably similar in shape and size regardless of expiratory effort. This limitation of expiratory flow over most of the lung volume, independent of effort, is due to the dynamic compression of airways by intrathoracic pressure. As forced expiration proceeds from TLC to RV, airway resistance must be overcome, and the high pressures near the alveoli decline and reach atmospheric pressure at the mouth. The high intrapleural pressures generated collapse the downstream airways, and the pressure difference driving expiratory flow becomes alveolar minus intrapleural pressure instead of alveolar minus mouth pressure. In some highly-trained male endurance athletes, the mechanical limits for inspiratory and expiratory pressure development and flow generation can be reached during exercise [16]. There is also recent evidence to show that maximal expiratory flow is achieved during near-maximal exercise in endurance-trained female athletes

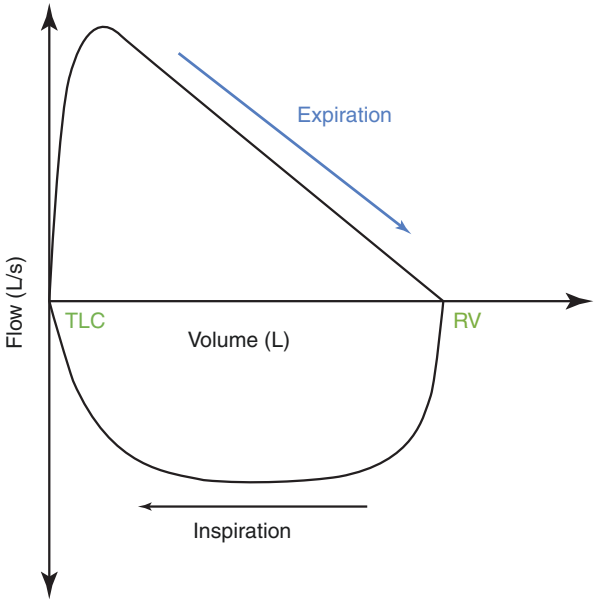

Fig. 1.1 Maximal flow-volume loop. *TLC* total lung capacity, *RV* residual volume

[17, 18]. The observation of expiratory flow limitation (EFL) during exercise in athletic humans suggests that the respiratory system is not without limits when the high ventilatory demands of strenuous exercise are superimposed.

1.4.3 Breathing Pattern

In addition to ensuring that blood gas homeostasis is maintained, the optimal breathing response also minimizes the amount of work required for a given $\dot{V}_A$. The amount of energy required to ventilate is referred to as the work of breathing (WOB). Important variables to consider for determining the mechanical WOB are tidal volume (V_T), breathing frequency (F_B), end-inspiratory lung volume (EILV), end-expiratory lung volume (EELV), flow rates, and duty cycle. The $\dot{V}_A$ is determined by the minute ventilation ($\dot{V}_E$) minus the dead space ventilation ($\dot{V}_D$). As the same level of $\dot{V}_E$ can be achieved with different combinations of V_T and F_B, a combination of these two variables must be established such that the increase in $\dot{V}_E$ is as efficient as possible and the $\dot{V}_D$ is minimized. At rest, inspiration occurs primarily due to diaphragm contraction, and expiration is passive. As $\dot{V}_E$ increases above rest, EELV falls due to recruitment of the expiratory abdominal muscles [19]. Recruitment of the abdominal muscles assists the inspiratory muscles in multiple ways. First, by reducing EELV, increases in V_T can occur on the linear portion of the respiratory system compliance curve [20]. Second, as EELV is reduced, the diaphragm is lengthened. Lengthening of the diaphragm allows it to function at a more optimal length for tension development, according to the length-tension relationship of the