# Respiratory System and Artificial Ventilation

Umberto Lucangelo • Paolo Pelosi
Walter A. Zin • Andrea Aliverti

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Springer

*Editors*
Umberto Lucangelo
Department of Perioperative Medicine
Intensive Care and Emergency
Cattinara Hospital
Trieste University School of Medicine
Trieste, Italy

Paolo Pelosi
Department of Clinical Science
University of Insubria
Varese, Italy

Walter A. Zin
Laboratory of Respiration Physiology
Carlos Chagas Filho Institute of Biophysics
Federal University of Rio de Janeiro
Rio de Janeiro, Brazil

Andrea Aliverti
TMB Laboratory
Department of Bioengineering
Politecnico di Milano
Milan, Italy

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# Preface

Intellectual undertakings, such as publishing a medical book—in this case, one concerning the respiratory tract and artificial support techniques—offer an important incentive for experts in a particular field, in that, as authors, they have the opportunity to share research results, whether their own or those of the working group they represent. Such books provide challenging and qualified updates to young researchers, who are thereby able to enhance their knowledge and working methods, for example, with the aim of improving the treatment standards of intensive-care patients.

The purpose of this book is to pursue the mission undertaken for the past thirty years by the Trieste University School of Anaesthesia and Intensive Care and, more recently, by the School of Anaesthesia and Intensive Care of Catania University.

The editors' task was made easier through a project promoted by the University of Catania, which involved the presence in Catania of my colleague Walter Zin, from Rio de Janeiro, who held a series of lectures and seminars on respiratory pathophysiology, aimed at teachers and students alike. Furthermore, important contributions by my colleagues Paolo Pelosi, from Varese; Andrea Aliverti, from Milan; and Umberto Lucangelo, from Trieste, must also be acknowledged. Their valuable co-operation and support contributed to achieving the high quality of this book.

The 18 chapters that make up this volume were written by highly regarded and internationally known clinical experts and researchers. To facilitate access to the information provided in the chapters, the volume has been subdivided into the following sections: Properties of the Respiratory System; Interaction Between the Pulmonary Circulation and Ventilation; Monitoring of Respiratory Mechanics, Acute Lung Injury–ARDS, Controlled Mechanical Ventilation in ARDS and the Open-Lung Concept; Nosocomial Pneumonia; Prone Ventilation;

Old and New Artificial Ventilation Techniques; Non-invasive Ventilation. 'Respiratory System and Artificial Ventilation' serves as a valuable tool for continuing medical education and for updating one's state-of-the-art clinical knowledge.

Venice, November 9, 2007

Antonino Gullo
Head and Chairman,
Department and School of Anaesthesia and Intensive Care,
University of Catania - Italy
Council, World Federation of Societies of Intensive and Critical Care Medicine (WFSICCM)

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# Contributors

Aliverti A.
TMB Laboratory, Department of Bioengineering, Politecnico di Milano, Milan, Italy

Antonaglia V.
Biomechanics Laboratory, Department of Perioperative Medicine, Intensive Care and Emergency, Azienda Ospedaliera-Universitaria, Trieste, Italy

Bacer B.
Department of Perioperative Medicine, Intensive Care and Emergency, Trieste University School of Medicine, Cattinara Hospital, Trieste, Italy

Beuret P.
Intensive Care Unit, Centre Hospitalier, Roanne, France

Blanch L.
Critical Care Center, Hospital de Sabadell, Institut Universitari Fundació Parc Taulí, Universitat Autònoma de Barcelona, Barcelona, Spain

Broccard A.F.
University of Minnesota, Medical Intensive Care Unit and Critical Care Division, Regions Hospital, St Paul, USA

Cagido V.R.
Laboratory of Respiration Physiology, Carlos Chagas Filho Institute of Biophysics, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

Calderini E.
Pediatric Intensive Care Unit, Department of Anesthesia and Critical Care, Fondazione Policlinico Mangiagalli Regina Elena IRCCS, Milan, Italy

Chidini G.
Pediatric Intensive Care Unit, Department of Anesthesia and Critical Care, Fondazione Policlinico Mangiagalli Regina Elena IRCCS, Milan, Italy

Chiumello D.
Institute of Anaesthesia and Critical Care, University of Milan, Policlinico IRCCS Hospital, Milan, Italy

Crimi E.
Interdepartmental Division of Critical Care Medicine, Division of Respirology, St. Michael's Hospital, University of Toronto, Canada

Del Sorbo L.
Interdepartmental Division of Critical Care Medicine, Division of Respirology, St. Michael's Hospital, University of Toronto, Canada

d'Onofrio D.
Department of Environment, Health and Safety, University of Insubria, Varese, Italy

Feihl F.
Division of Clinical Pathophysiology, Lausanne University Hospital (CHUV), Lausanne, Switzerland

Fontanesi L.
Department of Perioperative Medicine, Intensive Care and Emergency, Trieste University School of Medicine, Cattinara Hospital, Trieste, Italy

Gommers D.
Department of Anaesthesiology and Department of Intensive Care, Erasmus-MC, Rotterdam, The Netherlands

Gramaticopolo S.
Department of Perioperative Medicine, Intensive Care and Emergency, Trieste University School of Medicine, Cattinara Hospital, Trieste, Italy

Gruson D.
Department of Medical Intensive Care, University Hospital of Bordeaux, Bordeaux, France

Hilbert G.
Department of Medical Intensive Care, University Hospital of Bordeaux, Bordeaux, France

Lachmann B.
Department of Anaesthesiology, Erasmus-MC, Rotterdam, The Netherlands

Liapikou A.
Respiratory Intensive Care Unit, Pulmonology Department, Hospital Clinic of Barcelona, Barcelona, Spain

Lucangelo U.
Department of Perioperative Medicine, Intensive Care and Emergency, Cattinara Hospital, Trieste University School of Medicine, Trieste, Italy

Nagato L.K.S.
Laboratory of Respiration Physiology, Carlos Chagas Filho Institute of Biophysics, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

Pascotto S.
Biomechanics Laboratory, Department of Perioperative Medicine, Intensive Care and Emergency, Azienda Ospedaliera-Universitaria, Trieste, Italy

Pelosi P.
Department of Clinical Science, University of Insubria, Varese, Italy

Piller F.
Biomechanics Laboratory, Department of Perioperative Medicine, Intensive Care and Emergency, Azienda Ospedaliera-Universitaria, Trieste, Italy

Preis C.
Department of Anaesthesiology, Erasmus-MC, Rotterdam, The Netherlands

Ranieri V.M.
Department of Anaesthesia and Intensive Care Medicine, S. Giovanni Battista – Molinette Hospital, University of Turin, Turin, Italy

Santos F.B.
Laboratory of Respiration Physiology, Carlos Chagas Filho Institute of Biophysics, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

Torres A.
Respiratory Intensive Care Unit, Pulmonology Department, Hospital Clinic of Barcelona, Barcelona, Spain

Valencia M.
Respiratory Intensive Care Unit, Pulmonology Department, Hospital Clinic of Barcelona, Barcelona, Spain

Valente Barbas C.S.
Departamento de Cardio-Pneumologia e Patologia da Faculdade de Medicina da Universidade de São Paulo, Brazil

Vargas F.
Department of Medical Intensive Care, University Hospital of Bordeaux, Bordeaux, France

Voggenreiter G.
Department of Orthopaedic and Trauma Surgery, Hospitals in the Natural Parc Altmühltal, Eichstätt, Germany

Zin W.A.
Laboratory of Respiration Physiology, Carlos Chagas Filho Institute of Biophysics, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

# List of Abbreviations

| | |
|---|---|
| ALI | Acute lung injury |
| APCV | Adaptive pressure control ventilation |
| ARDS | Acute respiratory distress syndrome |
| ARDSexp | Extrapulmonary acute respiratory distress syndrome |
| ARDSp | Pulmonary acute respiratory distress syndrome |
| ARF | Acute respiratory failure |
| BAL | Bronchoalveolar lavage |
| BALF | Bronchoalveolar lavage fluid |
| BBS | Blind bronchial sampling |
| BiPAP | Bilevel positive airway pressure |
| BPD | Bronchopulmonary dysplasia |
| C | Compliance |
| CABG | Coronary artery bypass grafting |
| CHF | Congestive heart failure |
| CNAP | Continuous negative airway pressure |
| COPD | Chronic obstructive pulmonary disease |
| COX | Cyclooxygenase |
| CPAP | Continuous positive airway pressure |
| CPB | Cardiopulmonary bypass |
| CPG | Central pattern generator |
| CPIP | Chronic pulmonary insufficiency of prematurity |
| CPIS | Clinical pulmonary infection score |
| CPP | Cerebral perfusion pressure |
| CSA | Central sleep apnoea |
| CSF | Cerebrospinal fluid |
| CSR | Cheyne-Stokes respiration |
| CT | Computed tomography |
| CV | Conventional ventilation |
| DRG | Dorsal respiratory group |
| E | Elastance |
| ECMO | Extracorporeal membrane oxygenation |
| EELV | End-expiratory lung volume |
| EFL | Expiratory flow limitation |
| EHFO | External high-frequency oscillation |

| | |
|---|---|
| EIC | Electrical impedance tomography |
| ETA | Endotracheal aspiration |
| ETT | Endotracheal tube |
| FOT | Forced oscillation technique |
| FRC | Functional residual capacity |
| GGT | Galactosyl-hydroxylysylglucosyltransferase |
| HAP | Hospital-acquired pneumonia |
| HCAP | Health-care-associated pneumonia |
| HFOV | High-frequency oscillation ventilation |
| HFPV | High-frequency percussive ventilation |
| HFV | High-frequency ventilation |
| IAPV | Intermittent abdominal positive ventilation |
| ICP | Intracranial pressure |
| ICU | Intensive care unit |
| IL | Interleukin |
| iNOS | Inducible nitric oxide synthase |
| INPV | Intermittent negative-pressure ventilation |
| IPPV | Invasive positive-pressure ventilation |
| LAP | Left atrial pressure |
| LT | Leucotriene |
| MAP | Mean arterial pressure |
| MIP | Maximal inspiratory pressure |
| MIP-2 | Macrophage inflammatory protein-2 |
| MOD | Multi-organ dysfunction |
| MRSA | Methicillin-resistant *Staphylococcus aureus* |
| MS | Multiple sclerosis |
| NEEP | Negative end-expiratory pressure |
| NEP | Negative expiratory pressure |
| NICU | Neonatal intensive care unit |
| NIPPV | Non-invasive positive-pressure ventilation |
| NIV | Non-invasive ventilation |
| NO | Nitric oxide |
| NP | Nosocomial pneumonia |
| NPV | Negative-pressure ventilation |
| OEP | Optoelectronic plethysmography |
| OLC | Open lung concept |
| PAI | Plasminogen activator inhibitor |
| PAV | Proportional assist ventilation |
| PCV | Pressure control ventilation |
| PEEP | Positive end-expiratory pressure |
| PEEPi | Intrinsic positive end-expiratory pressure |
| Pga | Gastric pressure |
| PIP | Peak inspiratory pressure |
| $P_L$ | Transpulmonary pressure |
| PMM | Potentially multiresistant microorganism |

| | |
|---|---|
| Poes | Oesophageal pressure |
| PPV | Positive-pressure ventilation |
| PRG | Pontine respiratory group |
| PS | Pressure support |
| PSB | Protected telescopic catheter |
| $P_{TM}$ | Transmural airway pressure |
| PVR | Pulmonary vascular resistance |
| Pw | Abdominal wall pressure |
| R | Resistance |
| RARs | Rapidly adapting stretch receptors |
| RV | Residual volume |
| SARs | Slowly adapting stretch receptors |
| SIDS | Sudden infant death syndrome |
| SIRS | Systemic inflammatory response syndrome |
| sNIPPV | Synchronised nasal intermittent positive-pressure ventilation |
| TLC | Total lung capacity |
| TNF | Tumour necrosis factor |
| TREM | Triggering receptor expressed on myeloid cells |
| TTA | Transthoracic needle aspiration |
| VALI | Ventilator-associated lung injury |
| VAT | Ventilator-associated tracheobronchitis |
| $V_E$ | Minute ventilation |
| VILI | Ventilator-induced lung injury |
| VMR | Ventilatory muscle rest |
| VRG | Ventrolateral respiratory group |
| $V_T$ | Tidal volume |
| ZEEP | Zero end-expiratory pressure |

# Properties of the Respiratory System

# Control of Breathing

**F.B. Santos, L.K.S. Nagato, W.A. Zin**

## Introduction

The physiological control of the respiratory system is unique among organ systems. Breathing is essential to life and must occur 24 h a day, 365 days a year, in the conscious or unconscious state, awake or asleep. At the same time, humans and other mammals need to be able to temporarily interrupt the normal pattern of breathing to perform other functions, such as eating and vocalising [1]. The voluntary and involuntary control of the respiratory system is unequalled and a very complex process. This chapter will appraise some relevant issues to improve clinicians' understanding of the normal mechanism of breathing and its possible disorders in disease.

## Respiratory Control Components

Ventilation is constantly monitored and adjusted to maintain appropriate arterial pH and $PaO_2$. This homeostatic control system requires a set of sensors, a central controlling mechanism and an effector arm to carry out its commands (Fig. 1). Afferent information from sensors modulates the central command of respiratory muscles [2]. The brain constantly receives information from the upper airways, lungs and chest wall and decides how the ventilatory pump will respond.

### *Respiratory Sensors*

Afferent input into the central system is provided primarily by groups of neural receptors, either mechanoreceptors or chemoreceptors. The latter respond to alterations in $PaO_2$, $PaCO_2$ and pH.

U. Lucangelo, P. Pelosi, W.A. Zin, A. Aliverti (eds.) *Respiratory System and Artificial Ventilation*. 

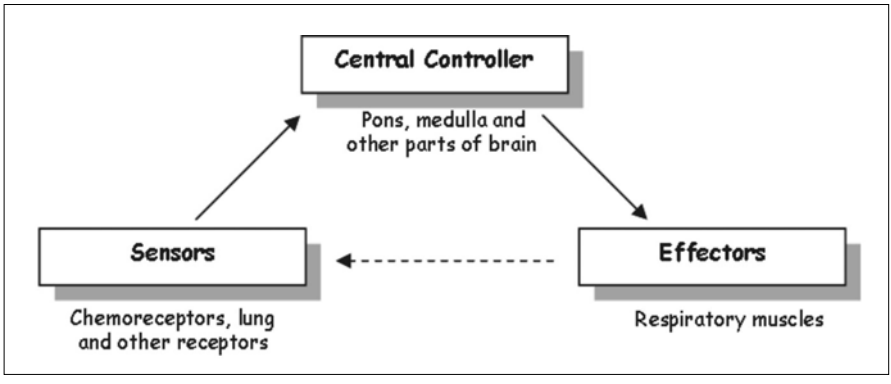


**Fig. 1** The control of breathing: basic elements. Sensors transmit information to the central controller. Subsequently, stimuli are sent to the effectors–the respiratory muscles–to adjust ventilatory responses. Adapted from [3]

## Peripheral Chemoreceptors

From their location in the carotid and aortic bodies, peripheral chemoreceptors direct the response to changes in $PaO_2$, $PaCO_2$ and pH. The carotid bodies are found at the bifurcation of the common carotid artery into the internal and external carotid arteries (Fig. 2) and their sensory supply reaches the brain via the glossopharyngeal nerve. The aortic bodies are located around the ascending aorta and send their afferent stimuli via the vagal nerves to the central nervous system. Since the arterial blood supply of these bodies amounts to approximately 2 l/min/100 g tissue (they are located on the outside of the main arteries and receive their own perfusion), they are one of the most highly perfused tissues in the human body [4,5]. The carotid and aortic bodies consist of two different cell types, glomus cells (type I) and sheath cells (type II). Afferent neurons terminate on glomus cells. There is also an unmyelinated supply to the sheath cells.

It is not clear how the carotid and aortic bodies sense hypoxaemia, but is clear that the stimulus for increased ventilation is $PaO_2$, not the oxygen content of the blood [1]. At normal levels of $PaO_2$, some neural activity arises from these chemosensors. At hyperoxic levels, this activity is only slightly reduced in normal people whereas in arterial hypoxaemia the intensity of the response varies in a non-linear manner according to the severity of the condition [7]. The greatest increase in activity in response to hypoxaemia occurs when $PaO_2$ falls to ≤60 mmHg or an $F_IO_2 \leq 0.1$ [1,7]. This increase in ventilation is manifested primarily by an increase in the depth of breathing (tidal volume or $V_T$) but an increased respiratory rate is also observed. These responses vary according to the degree of hypoxaemia.

In mammals, the carotid bodies account for about 90% of the ventilatory response to hypoxaemia; the remaining 10% arises from the aortic bodies. The former are also responsible for 20–50% of the response to arterial hypercapnia and acidaemia, with the remaining 50–80% of the response mediated by central brainstem receptors [8].

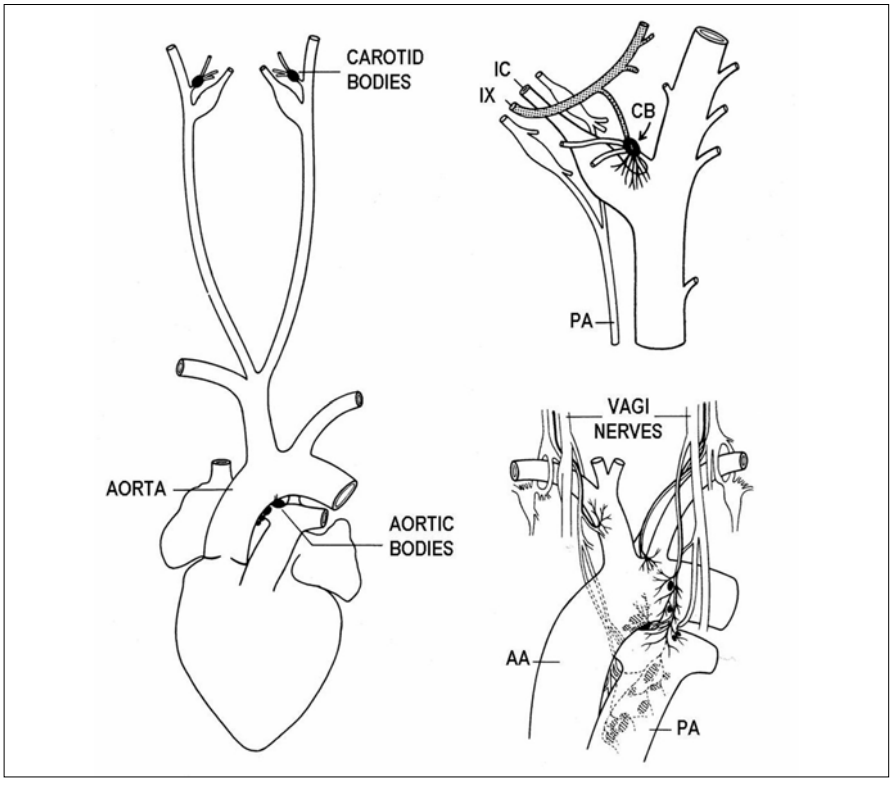


**Fig. 2** Sites where carotid and aortic bodies are located. *Left* Anatomical positioning of the carotid and aortic chemoreceptors. *Right, top* The sensory output of the carotid bodies (*CB*) reaches the brain via the glossopharyngeal nerve (*IX*); *X*, Vagus nerve; *IC*, internal carotid. *Right, bottom* Aortic chemoreceptors. *PA*, Pulmonary artery; *AA*, ascending aorta. Adapted from [6]

The activity of the peripheral chemoreceptors also increases with high levels of $PaCO_2$ and reduced levels of arterial pH, leading to increased ventilation. It is not immediately evident whether $PaCO_2$ and/or pH represent the stimulus under conditions of acute hypercapnia. Although responsive to changes in oxygen and carbon dioxide levels, the chemoreceptor is much more sensitive to acute hypercapnia than to hypoxaemia [7].

## Central Chemoreceptors

The fact that a ventilatory response to additional $CO_2$ persists in experimental animals despite peripheral chemoreceptor denervation suggests that there are chemoreceptors in the brain that are sensitive to $CO_2$ or hydrogen ions [9]. These receptors respond to changes in $PaCO_2$ (by increasing ventilation in response to

increased $PCO_2$ and vice versa) and pH (by increasing ventilation to a decreased pH and vice versa). Although no definite chemoreceptors have been defined anatomically, results of experiments involving the local application of chemical, electrical and thermal stimuli suggest that central chemoreceptors are located at or near the ventral surface of the medulla [9]. This location may facilitate the ability of the central chemoreceptors to monitor changes in $PaCO_2$ and pH levels in the cerebrospinal fluid (CSF). Hydrogen ions enter and are found in the CSF and extracellular fluid in the vicinity of the central chemoreceptors. The presence of these ions is a result of $CO_2$ dissociation and direct diffusion into and out of the bloodstream. Elevated arterial $CO_2$ easily crosses the blood–brain barrier because this gas is highly membrane-permeable, is converted to carbonic acid ($H_2CO_3$) and rapidly dissociates into $H^+$ and $HCO_3^-$ ions. As a result, $H^+$ rises in the CSF and interstitium in parallel with $PaCO_2$. This increased $H^+$ stimulates respiration by a direct action on the central chemoreceptors [1,10].

There is an interaction between the responses of the peripheral and central chemoreceptors. The blood–brain barrier exhibits different permeabilities to ions, such as $H^+$ (low permeability), and lipid-soluble molecules, such as carbon dioxide (high permeability). In an acidic environment, the peripheral chemoreceptors would trigger an increase in ventilation before the local environment in the fluid bathing the medulla reflected the acid pH in the blood. As ventilation increases owing to stimulation of peripheral chemoreceptors, $PaCO_2$ decreases. The environment of central chemoreceptors would rapidly reflect the lower $PaCO_2$, but only later sense the elevated $H^+$ concentration of the blood (because of the extra time needed for the $H^+$ ions to cross the blood–brain barrier) [10]. However, when $PaCO_2$ level is chronically elevated, as might occur in a patient with severe COPD, the activities of the peripheral and central chemoreceptors decrease within a few days, as pH normalises. At extremely high levels of carbon dioxide ($PaCO_2$>80–100 mmHg) an anaesthetic effect may be produced and ventilation decreases rather than increases. This occurs because a chronically elevated $PaCO_2$ results in renal compensation and consequent retention of $HCO_3^-$. This $HCO_3^-$ gradually diffuses through the blood–brain barrier and into the CSF, where it binds to the excess $H^+$ produced by the elevated $PaCO_2$, which balances the stimuli on ventilatory drive [10].

At moderate degrees of hypoxaemia—between 45 and 60 mmHg—ventilation rises moderately to about twice its normal level. Only when $PaO_2$ falls below 40 mmHg is there a sharp increase in ventilation. When hypercapnia occurs simultaneously with acute hypoxaemia, a synergistic effect results and ventilation rises substantially.

## Pulmonary Receptors

Pulmonary receptors can be found in the airways and lung parenchyma and are innervated by the vagus nerves.

– *Pulmonary stretch receptors* are slowly adapting stretch receptors (SARs) located among smooth muscle cells within the intra- and extra-thoracic air-

ways. These receptors are stimulated by pulmonary inflation and may play a role in the early termination of inspiration when tidal volume increases—Breuer-Hering inflation reflex [11]. In humans, this reflex is manifest only at a $V_T$ >3 l and seems to play a protective role in preventing excessive lung inflation. The SARs do not accommodate to a persistent stimulus, such as prolonged distension [12].

- *Irritant receptors* are also called rapidly adapting stretch receptors (RARs) and are located among the airway epithelial cells. RARs respond to noxious stimuli, such as dust, cigarette smoke and histamine [13]. They are concentrated in the carina and primary bronchi and are also believed to trigger cough [12]. During normal quiet breathing, their discharge does not depend on the phases of the breathing cycle (inspiration and expiration); therefore, these receptors do not seem to influence to any great extent the baseline breathing pattern at rest [14]. RARs also seem to trigger the augmented ventilation and sighs occurring sporadically during normal breathing, which help to prevent atelectasis of the air spaces [15]. They have also been described as taking part in the dyspnoea, bronchoconstriction and rapid and shallow breathing that occur in asthma [13,16,17].
- *C fibres* are unmyelinated fibres that carry information from a variety of receptors whose function is not totally understood [1]. Located within the airways, these receptors respond to either mechanical or chemical factors.
- *Chest-wall and muscle mechanoreceptors* respond to changes in length, tension or movement. The primary mechanoreceptors in the chest are the muscle spindles, tendon organs of the respiratory muscles and the joint proprioceptors. Afferent information from these receptors reaches the respiratory centres in the medulla [7]. Mechanoreceptors may also contribute to the increase in ventilation that occurs during the early stages of exercise [18]. Muscle spindles and tendon organs sense changes in the force of contraction of the respiratory muscles. While muscle spindles regulate muscle tonus, tendon organs have an inhibiting effect on inspiration. Joint proprioceptors sense the degree of chest-wall movement and may also influence the level and timing of respiratory activity [19].

## *Central Respiratory Controllers*

The central respiratory controllers are divided into the brainstem group (involuntary) and the cerebral cortex group (voluntary). The neural structures responsible for the automatic control of breathing are found in the medulla and pons. Two aggregates of neurons, termed the dorsal respiratory group (DRG) and the ventrolateral respiratory group (VRG), contain both inspiratory and expiratory neurons. The DRG seems to play an important role in processing information from receptors in the lungs, chest wall and chemoreceptors that modulate breathing. Neural activity from the DRG is important to activate the diaphragm and the VRG. The DRG also exhibits a role in determining breathing rhythm and in reg-

ulating the changes in diameter of the upper airway that occur with breathing by stimulating the muscles to expand the upper airway during inspiration [1,2,7]. The DRG is located in the nucleus of the tractus solitarius in the medulla and apparently represents the site of origin of the normal rhythmic respiratory drive, which consists of repetitive bursts of inspiratory action potentials [20]. The exact mechanism by which this rhythm is generated remains unknown. The VRG is located within the nucleus ambiguus (rostrally) and nucleus retroambiguus (caudally). It innervates respiratory effector muscles by the phrenic, intercostal and abdominal respiratory motoneurons [20].

In the pons, the pontine respiratory group (PRG) contains neurons that may contribute to the transitions or switching from inspiration to expiration. Damage to the respiratory neurons in the pons leads to an increase in inspiratory time, a decrease in respiratory frequency and an increase in tidal volume [1,2,7]. Nuclei so far located in the pons are the parabrachialis medialis and Kölliker-Fuse.

The breathing rhythm of the central pattern generator (CPG) has been explained as follows. Inspiration begins by the abrupt removal of inhibitory impulses to the DRG. An increased inspiratory motoneuron activity ensues in the form of a slowly augmenting ramp of signals that is suddenly terminated by an off-switch mechanism. During expiration, another burst of inspiratory neuronal activity takes place [21]. In fact, so many different bursting patterns can be detected in the respiratory neurons in the medulla and pons that, so far, any model or hypothesis of the triggering or interaction among the structures remains speculative.

The cerebral cortex may temporarily influence or bypass the central respiratory control mechanism in order to accomplish behaviour-related respiratory activity, such as cough, speech, singing and voluntary breath-holding [22,23]. Discomfort and anxiety may also influence the respiratory rhythm. When experiencing pain or shortness of breath, most people increase their respiratory rate, and total ventilation increases. The pattern of breathing may also reflect attempts to reduce the discomfort associated with ventilation. Patients with significantly reduced respiratory system compliance tend to breath with a rapid, shallow pattern. For patients with increased airway resistance, on the other hand, the high flow required for rapid, shallow breathing requires considerable work. These patients tend to adopt a slower breathing pattern with large tidal volumes [1].

## Neural Control of Smooth Muscle in the Airways

The autonomous nervous system importantly participates in the regulation of the calibre of the airways both in normal individuals and in those with pulmonary illness.

Cholinergic fibres (parasympathetic) penetrate between the muscle fibres of the bronchi and their stimulation results in the contraction of airway smooth muscle. Evidence for such an action stems from fact of that bronchodilatation ensues after sectioning of the vagus nerves and after the administration of anticholinergic drugs. The cholinergic system participates in the maintenance of the

bronchial tonus at rest and in the majority of bronchoconstriction cases. In contrast, the smooth muscle fibres in the airways present adrenergic innervation. While the amount of α-adrenoreceptors is reduced and their role seems insignificant, β-adrenoreceptors antagonise bronchoconstriction in asthmatic patients, by promoting the relaxation of airway smooth muscle [23].

Evidences show that the airways contain a system of innervation in which the neurotransmitters are neither adrenergic nor cholinergic. This system is known as non-adrenergic non-cholinergic innervation (NANC). Its location cannot be distinguished morphologically from those of the classic sympathetic and parasympathetic ways, but its stimulation can result in an excitatory response but its stimulation can result in a non-adrenergic non-cholinergic excitatory or inhibitory response. Among the neurotransmitters of this system, neuropeptides, such as substance P and neurokinin A, among others, can be found [24].

### *Effector System*

The pathways and muscles involved in the actual performance of inspiration and expiration make up the effector system. The spinal descending pathways connect the DRG and VRG to the ventrolateral columns of the spinal cord; finally, the stimuli reach the α-motoneurons leading to the diaphragm, intercostal and abdominal muscles, and to other muscles promoting respiratory movements.

The respiratory muscles encompass the diaphragm and the intercostal, abdominal and accessory muscles of respiration. The diaphragm is responsible for the majority (75%) of gas movement during quiet inspiration, while the parasternal internal intercostals and scalenes account for the remainder [25].

## Control of Breathing in Disease

### *Chronic Obstructive Pulmonary disease*

The patient with chronic obstructive pulmonary disease (COPD) presents altered V'/Q' distribution with hypoxaemia, with or without $CO_2$ accumulation. Airflow obstruction could be the most important fact to explain the hypercapnia in COPD patients. Inspiratory muscle dysfunction and the coexistence of nocturnal hypoventilation may worsen the hypercapnia. However, the true reason that some patients present with $CO_2$ retention while others do not, despite the same degree of obstruction, remains unknown. The native ventilatory response to $PaCO_2$ might constitute an inter-individual factor contributing to the variable hypercapnia in COPD patients. This concept of inherent differences in the ventilatory response to $CO_2$ arose from observations of the considerable variability in the magnitude of the ventilatory response to experimentally induced increases in arterial $PCO_2$ in normal subjects. According to this paradigm, COPD patients have been classi-

fied into those with high ventilatory responses to abnormal blood gases ('pink puffers') and those with low responses ('blue bloaters') [26].

Another factor that may contribute to the variable arterial $CO_2$ retention in severe COPD patients is a corresponding coincidence of sleep-related hypoventilation: patients with a larger amount of sleep-disordered breathing have daytime hypoventilation and those with normal ventilation during sleep only slight hypoventilation. Additionally, patients with obstructive sleep apnoea syndrome and concurrent COPD have higher daytime $PaCO_2$ values than patients without COPD [27].

The effects of a high inspiratory oxygen fraction are still controversial. Some patients with $CO_2$ retention worsen their respiratory acidosis when they inhale high $O_2$ concentrations. This effect is usually explained by the loss of the hypoxic stimulus to breathing. However, a reduction in the hypoxic ventilatory drive may not be the only mechanism inducing hypercapnia in these patients. The worst V'/Q' mismatch results in a significantly increased dead space; this is another explanation for the arterial hypercapnia associated with supplemental oxygen administration. Prior to the use of supplemental oxygen, areas of local alveolar hypoxia produce pulmonary hypoxic vasoconstriction, thereby diverting the flow of $CO_2$-rich blood from poorly ventilated to better aerated lung segments. When supplemental oxygen reverses local hypoxaemia, pulmonary hypoxic vasoconstriction nullifies and allows the perfusion of very poorly ventilated lung segments, increasing the dead space and reducing the effective alveolar ventilation. As a result, arterial $CO_2$ rises. Finally, $PaCO_2$ may increase in the face of supplemental oxygen administration because of a concurrent decrease in the $CO_2$ carrying capacity of the haemoglobin molecule secondary to the increasing oxygenation. This results in an altered steady-state relationship between carbaminohaemoglobin and $PaCO_2$, which raises the latter by several millimetres of mercury. This is known as the Haldane effect [28].

COPD patients exhibit an increased neural drive to their respiratory muscles that seems to be larger in hypercapnic COPD patients than in normocapnic patients. This increased respiratory drive is probably needed to overcome both increased airway resistance and mechanically disadvantaged respiratory muscles [26,29].

## *Neurological Diseases*

Respiratory dysfunction may constitute an early and relatively major manifestation of several neurological disorders, including structural or degenerative ailments of the central or peripheral nervous system or metabolic encephalopathies [30]. Neuromuscular diseases are often associated with abnormalities of ventilatory control and their associated hypoventilation, particularly during sleep, and with a reduced ventilatory response to $CO_2$ and $O_2$ [30,31]. Such patients increase their respiratory rate rather than $V_T$ in response to hypercapnia and hypoxaemia. This rapid and shallow breathing response is thought to be an attempted compensation aimed at increasing ventilation with minimal increase

in the work of breathing. Tachypnoea may then worsen respiratory muscle fatigue, leading to a further reduction in tidal volume. Respiratory failure typically complicates advanced neuromuscular disease by compromising effective respiratory muscle function. Death in these patients is usually due to progressive respiratory failure and superimposed infections secondary to aspiration resulting from pharyngeal dysfunction [30,31].

Respiratory control may be affected acutely or subacutely, as in stroke or multiple sclerosis. Lesions affecting the PRG, DRG, VRG or chemoreceptors may express an abnormal respiratory rhythm, central alveolar hypoventilation or both. A unilateral lesion of the lateral medulla, including the VRG, leads to blunting of the ventilatory response to $CO_2$ and sleep apnoea syndrome, particularly when there is another predisposing factor such as nasal septum deviation. Cheyne-Stokes respiration typically accompanies bilateral infarcts of the cerebral hemispheres, but also occurs in infratentorial ischaemic stroke [30,31].

Multiple sclerosis (MS) may yield respiratory dysfunction, in general associated with large lesions involving the upper cervical cord or medulla. Acute demyelinating lesions involving the dorsolateral medulla may result in loss of automatic breathing, usually associated with impaired swallowing and cough reflex. Thus, there ensues a risk of aspiration pneumonia [30,31]. Paroxysmal hyperventilation may occur as a manifestation of an acute lesion in the upper brainstem. Bulbar weakness, leading to aspiration followed by bronchopneumonia, is common in the terminal stages of MS. More rarely, loss of response to $CO_2$ and hypercapnic respiratory insufficiency may occur early in the course of the disease [30,31].

Brainstem tumours may produce central neurogenic hyperventilation, central sleep apnoea, irregular breathing, short breath-holding time and apneustic breathing. Occasionally, abnormalities of respiratory control are the only manifestations of the tumour and resolve after its resection. Patients with severe traumatic brainstem or high cervical-cord injury may lose both voluntary and autonomic control of breathing. These patients require ventilatory support, which is given via a tracheostomy through which tracheal suction can also be performed [30,31].

## *Sudden Infant Death Syndrome*

Sudden infant death syndrome (SIDS) is, according to the newly proposed definition: 'The sudden unexpected death of an infant <1 year of age, with onset of the fatal episode apparently occurring during sleep, that remains unexplained after a thorough investigation, including performance of a complete autopsy and review of the circumstances of death and the clinical history' [32]. Despite the fact that the diagnosis of SIDS originates from the exclusion of known causes of death, there are common features in most cases. These observations have led to the introduction of a triple-risk model for the understanding of SIDS. The model proposed in 1993 implies that SIDS only occurs if three conditions occur simultaneously: a vulnerable developmental stage of the CNS and the immune system;

predisposing factors, including a certain genetic pattern; and trigger events, such as sleeping position, maternal smoking, or infection [32]. Despite many studies in this area, the real aetiology of SIDS remains unknown.

Abnormal functioning of the central chemoreceptors represents one of the possible mechanisms generating SIDS. The recently born with apparently lethal episodes and the victims of SIDS studied before death presented a ventilatory pattern that was depressed with respect to the hypercapnic stimulus. Additionally, infants with episodes of apnoea in infancy present a slightly higher $PaCO_2$ as well as a lower sensibility to $CO_2$ as a trigger alert during sleep. The arcuate nuclei in the ventral medulla oblongata have been closely studied in SIDS victims. They are integrative sites for vital autonomic functions, including breathing and arousal, and are integrated with other regions that regulate arousal and autonomic chemosensory function. Quantitative three-dimensional anatomical studies indicated that some SIDS victims show hypoplasia of the arcuate nuclei, and as many as 56% of SIDS victims exhibit histopathological evidence of less extensive bilateral or unilateral hypoplasia. Studies on neurotransmission in the arcuate nuclei have also identified receptor abnormalities in some SIDS victims that involve several receptor types relevant to state-dependent autonomic control overall and to ventilatory and arousal responsiveness in particular. These deficits include significant decreases in binding to muscarinic, cholinergic and serotonergic receptors [33].

## *Cheyne-Stokes Respiration*

Cheyne-Stokes respiration (CSR) with central sleep apnoea (CSA) is a breathing disorder seen in patients with advanced congestive heart failure (CHF). It is characterised by central apnoeas and hypopnoeas that alternate with periods of increasing-decreasing tidal volume. CSR-CSA has been associated with increases in sympathetic nervous activity in CHF patients, which is an important predictor of CHF progression, arrhythmias and mortality. Indeed, CSR-CSA, independent of other risk factors, elevates the risk of mortality in CHF by two- to three-fold. Successful treatment of CSR by continuous positive airway pressure (CPAP) leads to a significant reduction in sympathetic nervous activity and may reduce mortality by up to 40% in patients with CHF and CSR-CSA. Since CPAP has salutary effects on cardiac function (independent of its effect on CSR), it remains uncertain whether CSR-CSA is a mere phenomenon of a failing heart or a major contributor to poor outcomes in patients with CHF. Supplemental oxygen may be used as treatment and tends to eliminate or decrease CSR in CHF by eliminating hypoxaemia, which contributes to respiratory cycling [34]. The classic cases of CSR are caused by CNS dysfunction, such as a cerebrovascular accident. In this setting, CSR is usually associated with bilateral supramedullary damage in conjunction with a depressed level of consciousness, such as occurs during sleep, sedation or diffuse cortical injury [35].

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# Elastic and Resistive Properties of the Respiratory System

**W.A. Zin**

## Introduction

This chapter will consider basic aspects of respiratory-system mechanics in order to provide a background for the analysis of the most common disorders related to the elastic and resistive components of the lung and chest wall. Excellent reviews articles can be consulted, if further details are desired [1–9b].

The movements of the lungs are entirely passive. Forces must be applied to the respiratory system to move it from its resting position at the end of expiration. In spontaneous breathing, the respiratory muscles provide the external forces, whereas artificial ventilation moves the relaxed respiratory system. In either situation, movement depends on the impedance of the lung and chest wall, the two components of the respiratory system. This impedance stems mainly from the elastic and resistive mechanical properties that are found in the lung and in the chest wall. The inertial component of gas and tissue is usually negligible [10].

## Elastic Properties

Both the lungs and the chest wall can be considered as elastic structures, with transmural pressure gradients corresponding to stress and lung volume to strain. Over a certain range of volumes and pressures, lung and chest-wall structures obey Hooke's law, and the change in lung and chest-wall volumes divided by the transmural pressures required to produce them defines the compliance (C). Elastance (E) is the reciprocal of compliance, i.e. $\Delta P/\Delta V$, and is usually expressed in $cmH_2O$ per litre. Stiff structures present a high elastance. Respiratory-system elastance equals the sum of lung plus chest wall elastances (Ers=EL+Ew, respectively), whereas respiratory-system compliance is more complex: 1/Crs=1/CL+1/Cw.

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## *Pleural Pressure*

Since variations in lung and chest wall volumes are virtually identical, the compliances of the respiratory system, lung and chest wall vary according to the change in the transmural pressure (i.e. inside minus outside pressures) across these structures. Under static conditions, the distending pressure of the respiratory system (Prs), lung (PL) and chest wall (Pw) are (Fig. 1):

$$PL = Palv - Ppl \quad \text{(Eq. 1)}$$

where Palv represents the alveolar pressure [which is equal to the airway pressure (Paw) or pressure at the airway opening (Pao) under static conditions and in the face of an open glottis] and Ppl stands for intrapleural pressure. PL is commonly referred to as the transpulmonary pressure:

$$Pw = Ppl - Pbs \quad \text{(Eq. 2)}$$

where Pw represents the transthoracic or chest-wall pressure, and Pbs the pressure at the body surface (usually barometric pressure);

$$Prs = PL + Pw \quad \text{(Eq. 3)}$$

or

$$Prs = Palv - Ppl + Ppl - Pbs = Palv - Pbs \quad \text{(Eq. 4)}$$

As can be easily understood, precise determination of swings in intrapleural pressure is of paramount importance when it is necessary to divide respiratory

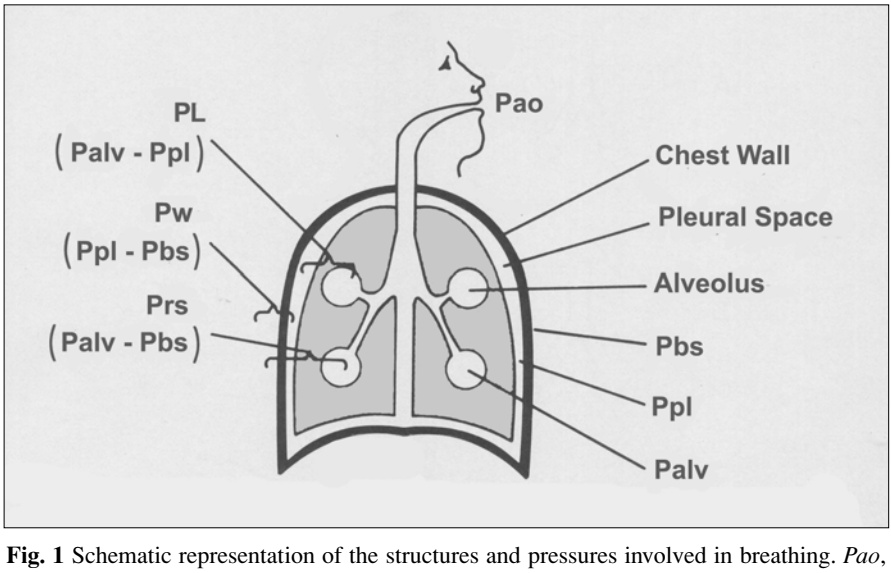


**Fig. 1** Schematic representation of the structures and pressures involved in breathing. *Pao*, Pressure at the airway opening; *Pbs*, pressure at the body surface; *Ppl*, intrapleural pressure; *Palv*, alveolar pressure; *PL*, transpulmonary pressure; *Pw*, chest-wall pressure; *Prs*, pressure difference across the respiratory system

system mechanics into their lung and chest-wall components. However, in clinical practice, pleural pressure is rarely measured because of all the risks involved in the procedure. Instead, variations in oesophageal pressure (Poes) are determined as these reflect quite accurately the changes in pleural pressure. Usually a latex balloon or a liquid-filled catheter is placed in the lower third of the oesophagus and its correct positioning must be accomplished to achieve a perfect reading of the changes in intrathoracic pressure [11]. Complete descriptions of the techniques used to measure Poes can be found in the literature [12–14].

## *Elastic Recoil of the Lungs*

The elastic recoil of the lungs tends to bring them down to their minimum volume. Accordingly, the elastic component (Pel,rs) of the total pressure applied to the respiratory system during inspiration is restored during expiration to promote expiration. In other words, the potential energy stored during inspiration returns to the system as kinetic energy. The passive volume–pressure curve of the lung is almost linear (constant compliance) up to volumes around 80% of the total lung volume. Beyond this point the curve flattens (compliance decreases) mainly because the elastic limit of the lung is approached and the structures stiffen. If transpulmonary pressure rises above 30 $cmH_2O$, the danger of tissue rupture may ensue.

### Tissue Recoil

Two components account for the elastic recoil of the lungs [15]. One of them is represented by the elastic components of lung tissue (mainly collagenous and elastic fibres). It is believed that the elastic behaviour of the lung does not depend strongly on the elongation of these fibres, but mainly on their geometric arrangement. The network of pulmonary connective tissue interconnects all pulmonary structures (vessels, bronchioles, alveoli, and so forth) and, as a result, they dilate during inspiration. This phenomenon is known as interdependence and contributes to keep the alveoli open, since if some of them collapsed, their neighbours would tether their walls, tending to reopen them. In addition to their tissue elastic properties, the lungs present another component that contributes importantly to their elastic characteristics: the surface tension of the liquid lining the alveoli and distal air spaces.

## *Surface Tension*

The air-liquid interface of the thin film of liquid that covers the surface of terminal respiratory units and probably also lines the luminal surface of terminal bronchioles displays surface tension, i.e. the molecules in the film attract each other along its surface. This component must also be overcome during inspiration: