Mechanics of Breathing:
Pathophysiology, Diagnosis and Treatment
Mechanics of Breathing:
Pathophysiology, Diagnosis and Treatment
Research on the mechanics of breathing has gained important new insights in human physiology that has advanced the practice of respiratory medicine. The new knowledge has markedly improved our understanding of pathophysiology, diagnosis, treatment and rehabilitation of diseases like chronic obstructive pulmonary disease (COPD), asthma, and acute respiratory failure.

In the field of asthma there is currently a major controversy between the molecular and cellular biologists, who focus on airway inflammation as the solution to this disease, and experts in lung mechanics who feel that the disease will not be controlled until the mechanics of excessive airway narrowing that characterize asthma is understood. Whatever is the case, it is of fundamental importance to understand how and why mechanisms protecting against excessive airway narrowing are lost in asthma. Solving the problem of asthma will almost certainly require collaborative efforts between cell and molecular biologists and respiratory physiologists to determine how airway inflammation alters airway structure and geometry, the load the airway and parenchyma impose on airway smooth muscle whose structure and function may be abnormal, and how these abnormalities combine to lead to excessive airway narrowing.

While up to now understanding the mechanics of breathing has failed to solve the major problems of COPD, it has certainly improved diagnosis by demonstrating that the disease is characterized by small airways obstruction, expiratory flow-limitation and loss of lung elastic recoil, thereby pinpointing where potentially effective therapies should be directed. An area where the mechanics of breathing is crucially important is the evaluation of lung volume reduction surgery for emphysema and the development of tests of mechanical function that will predict which patients will benefit. Shortness of breath and exercise limitation is the reason why COPD is so incapacitating. These are problems which must be understood if new therapies are to be successful. Recent studies suggest that interactions between ventilatory, skeletal muscle and circulatory mechanics seem to play a fundamental role.

Measurements of lung mechanics are necessary to determine whether therapy improves mechanical function and they are essential in determining the natural history of many respiratory diseases. Finally, mechanics of breathing is having a major impact on intensive care medicine resulting in the intelligent use of mechanical ventilation, understanding of the mechanical problems of ventilation through endotracheal tubes, the concept of barotrauma, the benefits of
permissive hypercapnia, and of new modes of mechanical ventilation.

Although in recent years the attention of reductionists to cellular and molecular mechanisms has been at the forefront of respiratory biology, we strongly believe that the complexity of the respiratory system must be still investigated by an integrative physiological approach. The study of molecules and cells, while stunningly successful, tells us little about how the molecules and cells interact in the whole integrated system to produce breathing and gas exchange. In future, efforts must be devoted to integrate cell and molecular biology with traditional respiratory physiology. The complex interactions between cells and molecules and how these influence the mechanics of breathing should be a fruitful area of future research.

We also believe that further advances in the field of ventilatory mechanics are dependent on two required elements: technologic innovations in the measurement systems and modeling so that the measurements can be interpreted. A framework or model to interpret the data and the proper measurement technique combine to advance a field of knowledge.

This book was envisioned as a state-of-the-art description of the complexity of both the normal and pathological respiratory system, mainly from the point of view of airway, lung and chest wall mechanics. The intention of the book is to disseminate new insights in the mechanics of breathing obtained by innovative methods of imaging and measuring the respiratory system, together with new emerging concepts in physiology and pathophysiology. For this purpose, it was necessary to have a multidisciplinary approach to combine the contributions of basic scientists in respiratory physiology and medicine, chest and intensive care physicians, and bioengineers involved both in modeling and instrumentation.

The book is structured into four parts. The first is dedicated to provide new basic concepts on airway, lung, chest wall and respiratory muscle mechanics during spontaneous breathing and exercise. In the second part, the chapters deal with emerging methods of assessing respiratory function: CT scanning, dynamic MRI, PET, SPECT, ultrasound, optoelectronic plethysmography, forced oscillations, gas washout, and evaluation of sensation. In the third part, COPD and asthma are treated from various points of view including basic pathology, pathophysiological mechanisms of airway obstruction and flow limitation, new indicators for diagnosis, and the response to pharmacological treatment. Finally, the last part is dedicated to emerging concepts in the field of assisted ventilation and respiratory failure. These concepts include trends in invasive and non-invasive mechanical ventilation, functional electrical stimulation, and innovative measurement methods.

The volume is based on a series of lectures delivered during the PostGraduate Course "What is new in mechanics of breathing: implications for diagnosis and treatment", held in Como, Italy in April 2001. On that occasion, many exciting lectures were delivered which generated lively discussion. We hope that this book will stimulate the same intellectual excitement.

ANDREA ALIVERTI, VITO BRUSASCO, PETER T. MACKLEM, ANTONIO PEDOTTI
# Table of Contents

**PHYSIOLOGY**

**Chapter 1 – The Act of Breathing**  
P.T. MACKLEM .................................................. 3

**Chapter 2 – The Work of Breathing During Exercise: Implications for Performance**  
L.M. ROMER, J.A. DEMPSEY .................................. 11

**Chapter 3 – Airway Physiology**  
V. BRUSASCO ..................................................... 25

**Chapter 4 – Role of Airway Smooth Muscle Mechanical Properties in the Regulation of Airway Caliber**  
S.J. GUNST .......................................................... 34

**ASSESSMENT OF RESPIRATORY FUNCTION**

**Chapter 5 – Opto-electronic Plethysmography**  
A. ALIVERTI, A. PEDOTTI ........................................ 47

**Chapter 6 – Dynamic Magnetic Resonance Imaging - A Powerful Modality in Diagnosis and Management of Patients with Emphysema**  
K. CHIHARA, A. HIDAKA ........................................ 60

**Chapter 7 – Airway Geometry Determined by Acoustic Reflections**  
O.F. PEDERSEN ..................................................... 70

**Chapter 8 – Airway Imaging Determined by Technegas**  
R. PELLEGRINO ..................................................... 83
Chapter 9 – Sub-second Multi-Detector Spiral Computed Tomography for the Study of Structure-Function Relationships Within the Lung
E.A. HOFFMAN ................................................................. 90

Chapter 10 – Pulmonary Functional Imaging with Positron Emission Tomography
D. LAYFIELD, S. HARRIS, G. MUSCH, M. VIDAL-MELO, J. G. VENEGAS .............. 116

Chapter 11 – Gas Washout and Aerosol Bolus Techniques: Non-invasive Measures of Lung Structure and Ventilation Heterogeneity
S. VERBANCK, M. PAIVA ...................................................... 129

Chapter 12 – Oscillatory Mechanics
D. NAVAJAS, R. FARRÉ ....................................................... 146

Chapter 13 – Measurement of Respiratory System Impedances
R.L. DELLACA ................................................................. 157

Chapter 14 – Physiopathology of Dyspnea
G. SCANO, M. GRAZZINI, L. STENDARDI, F. GIGLIOTTI ............................. 172

PATHOPHYSIOLOGY OF AIRWAY OBSTRUCTION: COPD AND ASTHMA

Chapter 15 – Pathology of Chronic Obstructive Pulmonary Disease and Asthma
S. BARALDO, G. TURATO, B. BEHÉ, R. ZUIN, M. SAETTA ......................... 183

Chapter 16 – Structure-to-Function Relationships in Chronic Obstructive Pulmonary Disease and Asthma
V. BRUSASCO ................................................................. 194

Chapter 17 – Inspiratory Capacity and Exercise Tolerance in Chronic Obstructive Pulmonary Disease
J. MILIC-EMILI, C. TANTUCCI ............................................. 201

Chapter 18 – Flow Limitation During Exercise and Chronic Obstructive Pulmonary Disease
P.M.A. CALVERLEY ............................................................. 210
<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Authors</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>Pathophysiology of Chronic Obstructive Pulmonary Disease</td>
<td>B.R. Celli</td>
<td>218</td>
</tr>
<tr>
<td>20</td>
<td>Response to Bronchodilators</td>
<td>R. Pellegrino</td>
<td>232</td>
</tr>
<tr>
<td>21</td>
<td>Functional Imaging of Airway Distensibility</td>
<td>R.H. Brown</td>
<td>238</td>
</tr>
<tr>
<td>22</td>
<td>The Significance of Variability of Airway Obstruction in Asthma</td>
<td>C. Que, S. Kelly, G. Maksym, P.T. Macklem</td>
<td>249</td>
</tr>
<tr>
<td>23</td>
<td>Nitric Oxide in Asthma is Like Insulin in Type II Diabetes</td>
<td>S. Permutt</td>
<td>260</td>
</tr>
<tr>
<td>24</td>
<td>Use of Positive End-expiratory Pressure and Continuous Positive Airway Pressure</td>
<td>P. Pelosi, D. Chiumello</td>
<td>271</td>
</tr>
<tr>
<td>25</td>
<td>Non-invasive Mechanical Ventilation in Intensive Care Unit</td>
<td>N. Barbarito, E. De Mattia, S. Nava</td>
<td>281</td>
</tr>
<tr>
<td>27</td>
<td>Opto-electronic Plethysmography in the Intensive Care Unit</td>
<td>A. Aliverti</td>
<td>314</td>
</tr>
<tr>
<td>28</td>
<td>On-line Monitoring of Respiratory Mechanics</td>
<td>G. Nucci, M. Mergoni, G. Polese, C. Cobelli, A. Rossi</td>
<td>327</td>
</tr>
<tr>
<td>29</td>
<td>Oscillatory Mechanics During Mechanical Ventilation</td>
<td>R. Farré, D. Navajas</td>
<td>337</td>
</tr>
</tbody>
</table>
Chapter 30 – Mechanisms in Applications of Recruitment and Derecruitment in the Acute Respiratory Distress Syndrome
J.J. Marini ................................................................. 348

Chapter 31 – Emerging Problems in Mechanical Ventilation: the Prone Position
L.Gattinoni, D. Chiumello, P. Pelosi, M.L. Caspani ...................... 359

Subject Index ................................................................. 369
List of Contributors

A. Aliverti
Centro di Bioingegneria
Fondazione Don Gnocchi IRCCS and
Dipartimento di Bioingegneria
Politecnico di Milano, Italy

S. Baraldo
Dipartimento di Medicina Clinica
e Sperimentale, Divisione Malattie
Respiratorie, Università di Padova, Italy

N. Barbarito
Unità di Terapia Intensiva Respiratoria,
Fondazione Salvatore Maugeri,
Pavia, Italy

B. Beghé
Dipartimento di Medicina Clinica
e Sperimentale, Divisione Malattie
Respiratorie, Università di Padova, Italy

R.H. Brown
Departments of Anesthesiology and
Critical Care Medicine, Medicine, Johns
Hopkins University,
Baltimore, USA

V. Brusasco
Fisiopatologia Respiratoria,
Dipartimento di Medicina Interna,
Università di Genova, Italy

P.M.A. Calverley
Department of Medicine, Clinical Science
Centre, University Hospital Aintree,
Liverpool, UK

M.L. Caspani
Università degli Studi di Milano,
Istituto di Anestesia e Rianimazione,
Ospedale Maggiore Policlinico, IRCCS,
Milano, Italy

B.R. Celli
Chief Pulmonary and Critical Care
Medicine, St. Elizabeth’s Medical Center,
Tufts University, Boston, USA

K. Chihara
Department of Thoracic Surgery,
Shizuoka City Hospital, Shizuoka, Japan

D. Chiumello
Università degli Studi di Milano,
Istituto di Anestesia e Rianimazione,
Ospedale Maggiore Policlinico, IRCCS,
Milano, Italy

C. Cobelli
Dipartimento di Elettronica e Informatica,
Università di Padova, Italy

R.L. Dellaca’
Centro di Bioingegneria
Fondazione Don Gnocchi IRCCS and
Dipartimento di Bioingegneria
Politecnico di Milano, Italy

E. De Mattia
Unità Intensiva di Malattie Respiratorie,
Fondazione Salvatore Maugeri, Pavia, Italy

J.A. Dempsey
Department of Population Health
Sciences, University of Wisconsin,
Madison, USA

G. Exner
SCI Center, Hamburg, Germany

R. Farré
Unitat de Biofisica i Bioenginyeria,
Facultat de Medicina, Universitat de
Barcelona, Institut d’Investigacions
Biomèdiques August Pi Sunyer,
Barcelona, Spain
List of Contributors

L. Gattinoni
Universita degli Studi di Milano,
Istituto di Anestesia e Rianimazione,
Ospedale Maggiore Policlinico, IRCCS,
Milano, Italy

F. Gigliotti
Fondazione Don C. Gnocchi ONLUS
(IRCCS), Firenze, Italy

M. Grazzini
Fondazione Don C. Gnocchi ONLUS,
(IRCCS), Firenze, Italy

S.J. Gunst
Department of Cellular and
Integrative Physiology,
Indiana University School of Medicine,
Indianapolis, USA

S. Harris
Department of Anesthesia and Critical
Care, Massachusetts General Hospital,
Boston, USA

A. Hidaka
Department of Diagnostic Radiology,
Shizuoka City Hospital, Shizuoka, Japan

E.A. Hoffman
Department of Radiology,
University of Iowa College of Medicine,
Iowa City, USA

R. Jaeger
Research Service, Jr. VA Hospital, Hines,
USA; and Institute Jožef Stefan, Ljubljana,
Slovenia

F. Kandare
University Clinic of Respiratory and
Allergic Diseases, Golnik, Slovenia

S. Kelly
Meakins Christie Laboratories,
Montreal Chest Institute of the Royal
Victoria Hospital, McGill University
Health Centre, Montreal, Canada

D. Layfield
Department of Anesthesia and Critical
Care, Massachusetts General Hospital,
Boston, USA

P.T. Macklem
Meakins-Christie Laboratories,
Montreal Chest Institute of the Royal
Victoria Hospital, McGill University
Health Centre, Montreal, Canada

G. Maksym
Meakins Christie Laboratories,
Montreal Chest Institute of the Royal
Victoria Hospital, McGill University
Health Centre, Montreal, Canada

J.J. Marini
University of Minnesota, Minneapolis,
St. Paul, USA

M. Mergoni
Servizio di Anestesia e Rianimazione,
Azienda Ospedaliera di Parma, Italy

J. Milic-Emili
Meakins Christie Laboratories, McGill
University, Montreal, Quebec, Canada

G. Musch
Department of Anesthesia and Critical
Care, Massachusetts General Hospital,
Boston, USA

S. Nava
Dipartimento di Medicina Clinica
e Sperimentale, Divisione Malattie
Respiratorie, Università di Padova, Italy

D. Navajas
Unitat de Biofisica i Bioenginyeria,
Facultat de Medicina, Universitat de
Barcelona, Institut d'Investigacions
Biomèdiques August Pi Sunyer, Barcelona,
Spain

G. Nucci
Dipartimento di Elettronica e Informatica,
Università di Padova, Italy

M. Paiva
Laboratoire de Physique Biomédicale,
Université Libre de Bruxelles, Belgium

A. Pedotti
Centro di Bioingegneria
Fondazione Don Gnocchi IRCCS and
Dipartimento di Bioingegneria
Politecnico di Milano, Italy
List of Contributors

Ole F. Pedersen
Department of Environmental and Occupational Medicine, University of Aarhus, Denmark

R. Pellegrino
Servizio di Fisiopatologia Respiratoria, Azienda Ospedaliera S. Croce e Carle, Cuneo, Italy

P. Pelosi
Università degli Studi dell’Insubria, Dipartimento di Scienze Cliniche e Biologiche, Azienda Ospedaliera Universitaria, Ospedale di Circolo e Fondazione Macchi, Varese, Italy

S. Permutt
Division of Pulmonary and Critical Care Medicine, The Johns Hopkins Asthma and Allergy Center, Baltimore, USA

G. Palese
Unita Operativa di Pneumologia, Ospedali Riuniti di Bergamo, Italy

C. Que
Meakins Christie Laboratories, Montreal Chest Institute of the Royal Victoria Hospital, McGill University Health Centre, Montreal, Canada

L.M. Romer
John Rankin Laboratory of Pulmonary Medicine Department of Population Health Sciences, University of Wisconsin, Madison, USA

A. Rossi
Unità Operativa di Pneumologia, Ospedali Riuniti di Bergamo, Italy

M. Saetta
Dipartimento di Medicina Clinica e Sperimentale, Divisione Malattie Respiratorie, Università di Padova, Italy

G. Scano
Fondazione Don C. Gnocchi ONLUS (IRCCS), Firenze, Italy

U. Stanič
Institute Jožef Stefan, Ljubljana, Slovenia

L. Stendardi
Fondazione Don C. Gnocchi ONLUS (IRCCS), Firenze, Italy

C. Tantucci
Cattedra di Malattie dell’Apparato Respiratorio, Università di Brescia, Italy

G. Turato
Dipartimento di Medicina Clinica e Sperimentale, Divisione Malattie Respiratorie, Università di Padova, Italy

M. Vidal-Melo
Department of Anesthesia and Critical Care, Massachusetts General Hospital, Boston, USA

J.G. Venegas
Department of Anesthesia and Critical Care, Massachusetts General Hospital, Boston, USA

S. Verbanck
Respiratory Division, Academic Hospital, Vrije Universiteit Brussel, Belgium

R. Zuin
Dipartimento di Medicina Clinica e Sperimentale, Divisione Malattie Respiratorie, Università di Padova, Italy
Acknowledgements

This book is supported by two European Community funded actions under EC research programmes administered by the Commission of the European Communities.

The first action was the BREATH (Biomedical technology for REspiration Analysis THrough optoelectronics) RTD project (Contract n. BMH4-CT2363) under the Biomedical and Health Research programme - BIOMED2.

The second is the accompanying measure BREATH-PGC (PostGraduate Course) (contract n. QLK6-2000-30139) under Key Action 6 The Ageing and Disabilities, Quality of Life Research programme of the Fifth Framework programme for research.

The authors and editors wish also to thank the following companies for their support to the realization of this volume:

BTS SpA, Milan, Italy

GlaxoSmithKline Italia, Verona, Italy

SensorMedics Italia (Viasys Respiratory Technologies), Milan, Italy