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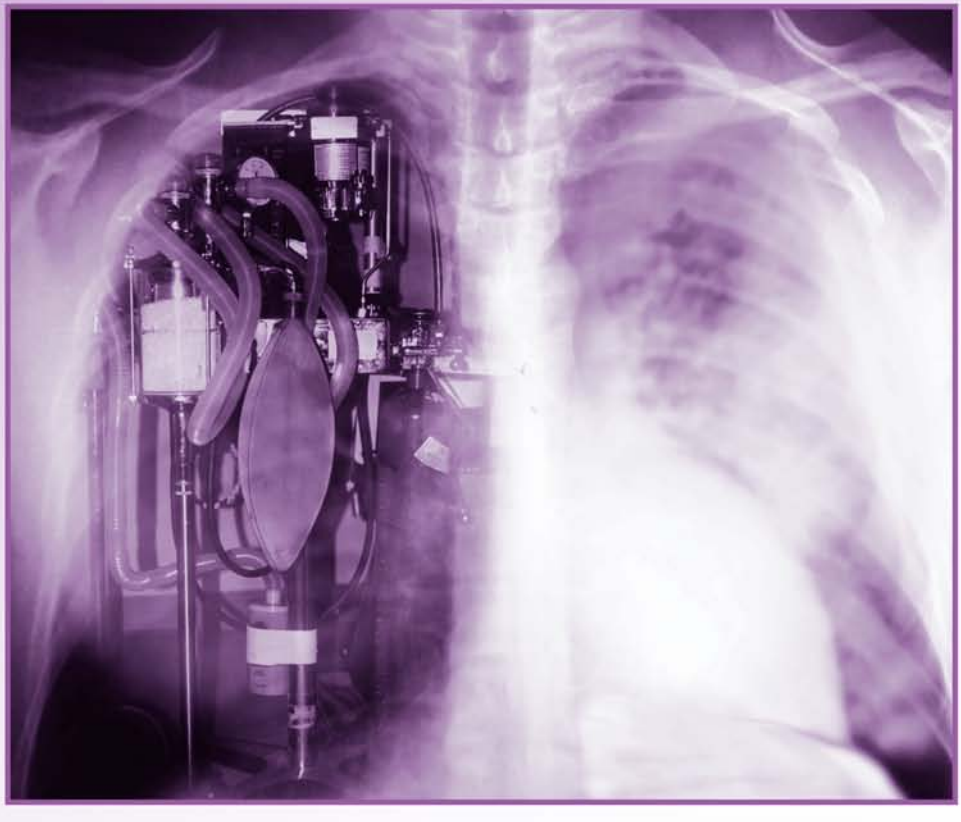
Ventilator-Induced Lung Injury



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Didier Dreyfuss
Georges Saumon
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Ventilator-Induced Lung Injury

LUNG BIOLOGY IN HEALTH AND DISEASE

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Claude Lenfant
Former Director, National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

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The opinions expressed in these volumes do not necessarily represent the views of the National Institutes of Health.

Ventilator-Induced Lung Injury

Edited by

Didier Dreyfuss
Paris 7-Denis Diderot Medical School
Paris, France
Hôpital Louis Mourier (Assistance Publique-Hôpitaux de Paris)
Colombes, France

Georges Saumon
Paris 7-Denis Diderot Medical School
Paris, France

Rolf D. Hubmayr
Mayo Clinic
Rochester, Minnesota, U.S.A.

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Introduction

But that life may in a manner of speaking be restored to the animal, an opening must be attempted in the trunk of the trachea, into which a tube of reed or cane should be put; you will then blow into this, so that the lung may rise again and the animal take in air.

—Andreas Vesalius (1514–1564) (1)

This appears to be the first report on artificial, or assisted, ventilation. Yet, a few years before Vesalius, Paracelus (1493–1541), a Swiss-born philosopher, had theorized the principles of resuscitation. It is unclear whether Vesalius had been inspired by the writings of Paracelus, or whether his demonstration of resuscitation was the result of his own creativity. Irrespective, it took generations for the work of these two luminaries to stimulate the application of artificial ventilation in humans.

In fact, it was the discovery of anesthesia in 1846 that provided the necessary impetus, plus about 60 years, in 1904, when Sauerbruch (2) developed his constant negative pressure chamber in order to prevent lung collapse during pulmonary surgery.

Today, mechanical ventilation has come to age, and that it assists, or replaces, spontaneous breathing is universally well recognized. Without doubt, it is the mainstay of intensive care medicine, and in many instances it is one of the essential tools of post-surgical care. The moment of triumph for mechanical ventilation came when acute respiratory distress syndrome was first described by Ashbaugh, Bigelow, and Petty in 1967 (3) and when it was established that mechanical ventilation was the essential therapy of the ensuing respiratory failure. Today, ventilators are one of the most used devices in medicine.

However, as is often the case with interventional therapies, there are some adverse consequences of mechanical ventilation. They are primarily

pulmonary, but they can also be more general, for example, impacting the kidney and the circulatory system. In order to realize the full benefit of mechanical ventilation, it is critical to have knowledge of these adverse events, and of their mechanisms.

This monograph, titled *Ventilator-Induced Lung Injury* and edited by Drs. Didier Dreyfuss, Georges Saumon, and Rolf D. Hubmayr, gives the reader a panoramic but detailed view of the pulmonary adverse consequences of mechanical ventilation. The authors, with international experience, are well known for their expertise in both fundamental and clinical investigations related to mechanical ventilation.

The series of monographs, Lung Biology in Health and Disease, has published many volumes focusing on lung diseases—especially acute respiratory distress syndrome—requiring mechanical respiratory assistance and several others on the approaches to mechanical respiration and management of ventilators. However, none have focused exclusively on the adverse consequences of mechanical ventilation. Thus, this volume is a most valuable addition to the series, and it should be of great interest to respiratory care physicians.

As the overall editor of the series, I am grateful to the editors and authors for giving us the opportunity to add this volume to the series.

Claude Lenfant, MD
Gaithersburg, Maryland, U.S.A.

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Preface

Few experimental findings have so sharply influenced the care of critically ill patients as has been the case with ventilator-induced lung injury. This breakthrough stemmed from a conceptual and experimental effort, stimulated by the need for improving the dismal prognosis of acute respiratory distress syndrome. One must remember the fatality rate of more than 90% (1) in initial clinical series and compare it with the 31% mortality rate observed with a lung protective strategy in the recent study from the Acute Respiratory Distress Syndrome Network (2) to realize the importance of the prognostic progress fostered by these experimental studies.

The pioneering study was published by Webb and Tierney (3), who showed that high peak airway pressure ventilation of intact rats provokes pulmonary edema. The lung lesions produced by this ventilation closely mimic those observed during acute respiratory distress syndrome (4,5). In other words, mechanical ventilators are potentially able to generate the disease they are supposed to support. Mead and coworkers (6), based on theoretical considerations, stressed that applying high pulmonary transmural pressure by ventilators to unevenly expanded lungs might cause

hemorrhages in hyaline membranes, only several years after the initial description of acute respiratory distress syndrome (7).

This book aims to describe the different steps of basic research that allowed the comprehension of ventilator-induced lung injury, their clinical consequences, and the new avenues of basic research that again emerged. Studies on mechanical transduction, lung mechanics, and endothelial and epithelial physiology formed the cornerstone of this better comprehension. This knowledge stimulated clinical research for designing safer ventilator studies, with overwhelming success for some strategies and persisting questions for others. Finally, new research efforts on the biology of inflammatory mediators during ventilator-induced lung injury and on gene therapy during acute lung injury set hope for further improvement of the prognosis for acute respiratory distress syndrome.

It was both a privilege and a pleasure for the three editors of this book to ask for the contributions of recognized experts in this field, and we wish to express our gratitude for their outstanding chapters, which will undoubtedly make this book a success.

Didier Dreyfuss
Georges Saumon
Rolf D. Hubmayr

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Contributors

Yochai Adir Division of Pulmonary Medicine, Carmel Medical Center, Technion, Institute of Technology, Haifa, Israel

Mircea Anghelescu Department of Pathophysiology, University of Medicine and Pharmacy, Timisoara, Timis, Romania

Steven M. Banks Critical Care Medicine Department, Warren G. Magnuson Clinical Center, National Institutes of Health, Bethesda, Maryland, U.S.A.

John A. Belperio Division of Pulmonary, Critical Care, and Hospitalists, David Geffen School of Medicine at UCLA, Los Angeles, California, U.S.A.

Anastacia M. Bilek Center for Devices and Radiological Health, Food and Drug Administration, Rockville, Maryland, U.S.A.

Karen J. Bosma Dipartimento di Anestesiologia e Rianimazione, Ospedale S. Giovanni Battista-Molinette, Universitá di Torino, Torino, Italy

Laurent Brochard Medical ICU, Henri Mondor Teaching Hospital, AP-HP, Paris 12 University, Créteil, France

Roy G. Brower Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, U.S.A.

Katherine J. Deans Critical Care Medicine Department, Warren G. Magnuson Clinical Center, National Institutes of Health, Bethesda, Maryland, and Department of Surgery, Massachusetts General Hospital, Boston, Massachusetts, U.S.A.

Kay C Dee Department of Applied Biology and Biomedical Engineering, Rose-Hulman Institute of Technology, Terre Haute, Indiana, U.S.A.

Didier Dreyfuss Paris 7-Denis Diderot Medical School, Paris, and Service de Réanimation Médicale, Assistance Publique-Hôpitaux de Paris, Hôpital Louis Mourier, Colombes, France

Peter Q. Eichacker Critical Care Medicine Department, Warren G. Magnuson Clinical Center, National Institutes of Health, Bethesda, Maryland, U.S.A.

Phillip Factor Pulmonary, Allergy, and Critical Care Medicine, Columbia University College of Physicians and Surgeons, New York, New York, U.S.A.

Vito Fanelli Dipartimento di Anestesiologia e Rianimazione, Ospedale S. Giovanni Battista-Molinette, Universitá di Torino, Torino, Italy

Niall D. Ferguson Interdepartmental Division of Critical Care Medicine and Department of Medicine, Division of Respirology, University Health Network and Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada

Leopoldo Ferrer Division of Pulmonary and Critical Care Medicine, University of Minnesota, Regions Hospital, St. Paul, Minnesota, U.S.A.

James A. Frank Cardiovascular Research Institute, University of California at San Francisco, San Francisco, California, U.S.A.

Bradley P. Fuhrman Division of Pediatric Critical Care, Department of Pediatrics, State University of New York at Buffalo and Women's and Children's Hospital of Buffalo, Buffalo, New York, U.S.A.

Joe G. N. Garcia Division of Pulmonary and Critical Care Medicine, Center for Translational Respiratory Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, U.S.A.

Donald P. Gaver III Department of Biomedical Engineering, Tulane University, New Orleans, Louisiana, U.S.A.

Andreas Günther Department of Internal Medicine, University of Giessen Lung Center (UGLC), Medical Clinic II, Justus-Liebig University School of Medicine, Giessen, Germany

David N. Hager Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, U.S.A.

Rolf D. Hubmayr Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, Minnesota, U.S.A.

Yumiko Imai Institute of Molecular Biotechnology of the Austrian Academy of Sciences (IMBA), Vienna, Austria

Anne-Marie Jacob Department of Biomedical Engineering, Tulane University, New Orleans, Louisiana, U.S.A.

Jeffrey R. Jacobson Division of Pulmonary and Critical Care Medicine, Center for Translational Respiratory Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, U.S.A.

Brian P. Kavanagh Departments of Critical Care Medicine and Anesthesia, Hospital for Sick Children, and University of Toronto, Toronto, Ontario, Canada

Michael P. Keane Division of Pulmonary, Critical Care, and Hospitalists, David Geffen School of Medicine at UCLA, Los Angeles, California, U.S.A.

John G. Laffey Department of Anesthesia and Intensive Care Medicine, Clinical Sciences Institute and National Centre for Biomedical Engineering Sciences, National University of Ireland and University College Hospital, Galway, Ireland

Emilia Lecuona Pulmonary and Critical Care Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, U.S.A.

Stéphanie Lehoux Inserm U689, Cardiovascular Research Center Inserm Lariboisière, Paris, France

Qin Lu Réanimation Chirugicale Polyvalente Pierre Viars, Hôpital Pitié-Salpêtrière, Assistance Publique Hôpitaux de Paris, Université Pierre et Marie Curie, Paris, France

John J. Marini Division of Pulmonary and Critical Care Medicine, University of Minnesota, Regions Hospital, St. Paul, Minnesota, U.S.A.

Philipp Markart Department of Internal Medicine, University of Giessen Lung Center (UGLC), Medical Clinic II, Justus-Liebig University School of Medicine, Giessen, Germany

Thomas R. Martin Pulmonary Research Laboratories, VA Puget Sound Health Care System, and Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of Washington School of Medicine, Seattle, Washington, U.S.A.

Michael A. Matthay Cardiovascular Research Institute, University of California at San Francisco, San Francisco, California, U.S.A.

Christian Mélot ICU, Erasme Teaching Hospital, Free University of Brussels, Brussels, Belgium

Alain Mercat Medical ICU, Angers Teaching Hospital, Angers, France

Peter C. Minneci Critical Care Medicine Department, Warren G. Magnuson Clinical Center, National Institutes of Health, Bethesda, Maryland, and Department of Surgery, Massachusetts General Hospital, Boston, Massachusetts, U.S.A.

Takashige Miyahara First Department of Internal Medicine, Shinshu University, Matsumoto, Nagano, Japan

Alan H. Morris Pulmonary and Critical Care Divisions, Department of Medicine, LDS Hospital and University of Utah School of Medicine, Salt Lake City, Utah, U.S.A.

Gökhan M. Mutlu Pulmonary and Critical Care Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, U.S.A.

Charles Natanson Critical Care Medicine Department, Warren G. Magnuson Clinical Center, National Institutes of Health, Bethesda, Maryland, U.S.A.

Margaret J. Neff Division of Pulmonary and Critical Care Medicine, Harborview Medical Center, University of Washington, Seattle, Washington, U.S.A.

Stephanie A. Nonas Division of Pulmonary and Critical Care Medicine, Center for Translational Respiratory Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, U.S.A.

Séverine Oudin Division of Medical Intensive Care, University Hospital of Geneva, Geneva, Switzerland

James C. Parker Department of Physiology, University of South Alabama College of Medicine, Mobile, Alabama, U.S.A.

Jérôme Pugin Division of Medical Intensive Care, University Hospital of Geneva, Geneva, Switzerland

V. Marco Ranieri Dipartimento di Anestesiologia e Rianimazione, Ospedale S. Giovanni Battista-Molinette, Universitá di Torino, Torino, Italy

Jean-Damien Ricard Service de Réanimation Médicale, Assistance Publique-Hôpitaux de Paris, Hôpital Louis Mourier, Colombes, France, Inserm U 722, Paris 7-Denis Diderot Medical School, Paris, France

Jean-Jacques Rouby Réanimation Chirugicale Polyvalente Pierre Viars, Hôpital Pitié-Salpêtrière, Assistance Publique Hôpitaux de Paris, Université Pierre et Marie Curie, Paris, France

Gordon D. Rubenfeld Division of Pulmonary and Critical Care Medicine, Harborview Medical Center, University of Washington, Seattle, Washington, U.S.A.

Clemens Ruppert Department of Internal Medicine, University of Giessen Lung Center (UGLC), Medical Clinic II, Justus-Liebig University School of Medicine, Giessen, Germany

Georges Saumon EA 3512, IFR 02 Claude Bernard, Paris 7-Denis Diderot Medical School, Paris, France

Daniel P. Schuster Departments of Internal Medicine and Radiology, Washington University School of Medicine, St. Louis, Missouri, U.S.A.

Werner Seeger Department of Internal Medicine, University of Giessen Lung Center (UGLC), Medical Clinic II, Justus-Liebig University School of Medicine, Giessen, Germany

Jeffrey M. Singh Interdepartmental Division of Critical Care Medicine and Department of Medicine, Division of Respirology, University Health Network and Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada

Arthur S. Slutsky Interdepartmental Division of Critical Care Medicine and Division of Respirology, Department of Medicine, University of Toronto, and Department of Critical Care Medicine, St. Michael's Hospital, Toronto, Ontario, Canada

Thomas E. Stewart Interdepartmental Division of Critical Care Medicine and Department of Medicine, Division of Respirology, University Health Network and Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada

Robert M. Strieter Division of Pulmonary, Critical Care, and Hospitalists, and Pathology and Pediatrics, Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, California, U.S.A.

Jacob I. Sznajder Pulmonary and Critical Care Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, U.S.A.

Alain Tedgui Inserm U689, Cardiovascular Research Center Inserm Lariboisière, Paris, France

Contents

1

Shear and Pressure-Induced Mechanotransduction

STÉPHANIE LEHOUX and ALAIN TEDGUI

Inserm U689, Cardiovascular Research Center Inserm Lariboisière
Paris, France

I. Introduction

Blood vessels are permanently subjected to mechanical forces in the form of stretch, encompassing cyclic mechanical strain due to the pulsatile nature of blood flow, and shear stress. Blood pressure is the major determinant of vessel stretch. It creates radial and tangential forces that counteract the effects of intraluminal pressure and affect all cell types in the vessel. In comparison, fluid shear stress results from the friction of blood against the vessel wall, and it acts in parallel to the vessel surface. Accordingly, shear is sensed principally by endothelial cells, strategically located at the interface between the blood and the vessel wall. Alterations in stretch or shear stress invariably produce transformations in the vessel wall that will aim to accommodate the new conditions and to ultimately restore the basal levels of tensile stress and shear stress (1,2). Hence, while acute changes in stretch or shear stress correlate with transient adjustments in vessel diameter, mediated through the release of vasoactive agonists or change in myogenic tone, chronically altered mechanical forces usually instigate important adaptive alterations of vessel wall shape and composition.

The concept of vascular remodeling has therefore been used to describe these transformations that occur in vessels undergoing mechanical stresses.

II. Mechanical Forces

On the basis of observations in chick embryos, Thoma in 1893 hypothesized that the diameter of blood vessels is regulated by the magnitude of blood flow, while the thickness of vessel walls depends on the magnitude of the forces of tension generated by blood pressure. This hypothesis has subsequently been experimentally confirmed. It has been demonstrated, for example, that the diameter of the abdominal aorta of a lamb undergoes a significant reduction between the 4th and 14th days postpartum (3). This reduction can be accounted for by a fall of approximately 70% in the blood velocity in the abdominal aorta at the time of delivery, due to the disappearance of the placental circulation, and is associated with apoptosis of vascular cells (4). Concurrently, the diameter of the thoracic aorta increases in parallel with the rise in systemic blood flow. Similarly, the thicknesses of the pulmonary artery and aorta, which are almost identical at birth due to the similarity in pressures in utero in both vascular territories, evolve differently after birth. The pulmonary artery atrophies during development, following the fall in pulmonary pressure postpartum, while the thoracic aorta thickens proportionately to the increase in systemic pressure (5).

A. Tension and Tensile Stress

Blood pressure produces strain on the vessel wall in a direction perpendicular to the endoluminal surface. This is counterbalanced by the intraparietal tangential forces in the longitudinal and circumferential directions exerted by different elements of the vessel wall, opposing the distending effects of blood pressure. The force per unit length of the vessel (the parietal tension, T) is related to the blood pressure (P) and the vessel radius (r) by Laplace's law:

$$T = Pr$$

The relation between circumferential tension and deformation of the vessel as intraluminal pressure increases depends on both the geometry and the elastic characteristics of its wall. The circumferential tension is actually borne by the total thickness of the arterial wall. Each element of the wall bears only a part of this tension. The tension per unit of thickness represents the stress exerted on the wall in the circumferential direction. It is expressed as:

$$T = Pr/h$$

where h is the thickness of the wall.

Numerous studies have demonstrated a direct relationship between the circumferential stress to which the vessel wall is exposed and the

structure of the wall itself (Fig. 1). When the stress increases due to an increase in arterial pressure, smooth muscle cell (SMC) hypertrophy and increases in collagen and elastin contents follow. Inversely, when the circumferential stress falls, the wall undergoes atrophy (6). Several physiologic and experimental arguments confirm the relationship between the circumferential stress and the thickness and composition of the vessel wall:

i. From one animal species to another, as the diameter of a particular blood vessel increases, the number of lamellar units and the total thickness of the wall increase proportionately, so that the circumferential stress remains constant irrespective of the size of the animal, from the rat to the horse. This "ideal" value is of the order of 2.106 dyne/cm^2 in the descending thoracic aorta (7). It varies according to the arterial territory and essentially depends on the structure of the blood vessel concerned.
ii. In all experimental models of arterial hypertension, a close correlation is observed between the level of arterial pressure and the frequency of polyploidy and hypertrophy of the SMCs of the arterial wall.
iii. SMC hypertrophy in the walls of the major arterial trunks develops only when the distending pressure has reached a threshold level, and never precedes the onset of hypertension, even when the neurohumoral abnormalities responsible for hypertension are already present.

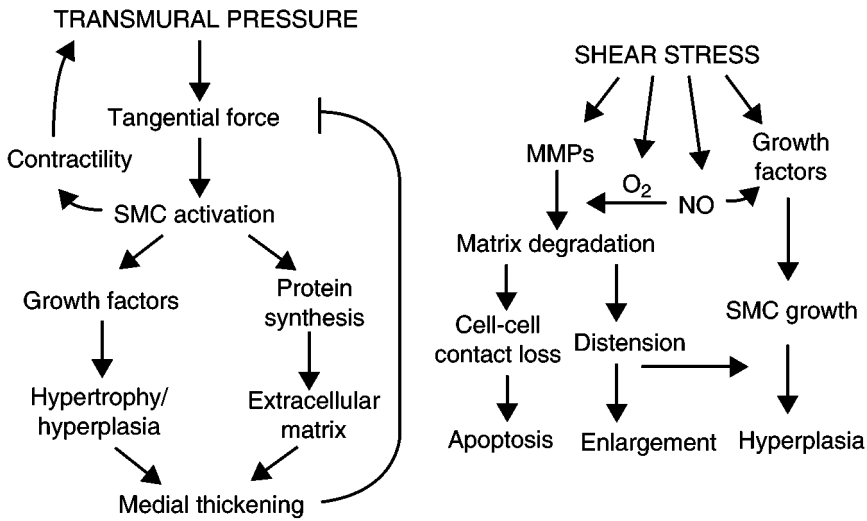

Figure 1 Sequence of vascular responses stemming from increased transmural pressure or shear stress and leading, through sequential events, to vascular remodeling.

The effects of mechanical tensile stress on the arterial wall have been extensively described and have been applied to the understanding of hypertension. Numerous animal and human studies have shown that sustained hypertension is associated with structural and functional alterations in both large arteries and arterioles. There is good evidence that hypertension is associated with increased arterial wall thickness (8), mostly due to SMC hypertrophy, accompanied by polyploidism, hyperplasia, and proportional changes in contractile and matrix proteins, leading to altered arterial function (9). According to Laplace's equation ($T = Pr/h$), the hypertrophy of the arterial wall compensates for the increase in blood pressure and contributes to maintaining a normal level of circumferential stress. In elastic and large conduit arteries, the adaptive response to hypertension serves to reduce and eventually normalize the tensile stress.

On the other hand, constant mechanical stimulation appears to be required for maintenance of normal contractile phenotype of SMC in the arterial wall. Vessels placed in conditions of abnormally low intraluminal pressure (10 mmHg) show decreased content, over three to six days, of smooth muscle marker proteins h-caldesmon and filamin content, compared with native vessels or aortic segments kept at physiological intraluminal pressure (80 mmHg) (10). Likewise, cyclic stretching of cultured airway SMC increases (in fact, prevents the decrease in) the expression of smooth muscle myosin heavy chains and myosin light chain kinase (11). Loss of stretch, together with loss of extracellular matrix contacts, is probably the major cause of differentiation of SMC in culture. Hence, a certain level of stretch is required to maintain vascular SMC (VSMC) in a quiescent state, but overstretching triggers adaptive processes resulting in increased protein synthesis and hypertrophy.

B. Shear Stress

As blood flows, it exerts a frictional force on the endothelial surface. This force is expressed as a shear stress (τ) on the endothelium, defined as the product of the blood viscosity and the blood-velocity gradient measured at the vessel wall. The shear stress transmitted to the endothelium by the blood flow tends to displace the endothelium and the intimal layer in the direction of flow (one might equally say that it is because the endothelium is fixed that friction occurs). In the case of laminar flow (where the profile of blood velocity is parabolic), shear stress is expressed as:

$$\tau = 4\mu Q/\pi r^3$$

where μ is the viscosity, Q the flow rate, and r the vessel radius. Note that the radius appears at the third power in the denominator. Thus, for a constant volume flow, a slight reduction in vascular diameter produces a much greater increase in shear stress.

Shear stress arising from the mechanical effects of blood flow on the vascular endothelium is also a determinant of arterial growth (Fig. 1). Under physiologic conditions, the mean shear stress to which the vascular endoluminal surface is exposed is remarkably constant, close to 10 to 15 dyne/cm^2, whatever the part of the arterial network considered, conductance or resistance arteries, and whatever the size of the animal (with the exception of the rat and the mouse in which the values are closer to 30 to 35 dyne/cm^2).

Shear stress–dependent remodeling can be illustrated by experiments where blood flow is either restricted or enhanced. In rabbits, the reduction in caliber of the developing carotid associated with a reduction in its blood flow is accompanied by a reduction in the elastin content of the carotid arterial wall (12). In contrast, the phenomenon of flow-dependent growth is best exemplified using the arteriovenous fistula model. In carotid–jugular arteriovenous fistulas, the flow rate in the developing carotids can be multiplied by a factor of up to 8. The chronic increase in shear tends to enhance the L-arginine/nitric oxide (NO) pathway in endothelial cells, and chronic inhibition of NO production by N^{ω}-nitro-L-arginine methyl ester (L-NAME) treatment inhibits, at least partially, the adaptive wall shear stress regulation in flow-loaded vessels (2). However, simple relaxation of VSMC alone cannot account for the very significant increase in vascular caliber observed, which may almost double in response to large increases in flow. Previous microscopic and ultrastructural studies of the arterial wall proximal to an arteriovenous fistula have shown extensive tears and fragmentation, as well as enlarged fenestrae, in the internal elastic lamina (IEL) (2,13,14), suggesting a potential role for matrix metalloproteinases (MMPs) in matrix digestion and reorganization leading to arterial wall remodeling. Indeed, increased blood flow in the rabbit carotid due to an arteriovenous shunt causes the release of MMP-2 and MMP-9, and chronic MMP inhibition prevents IEL fragmentation and adaptive remodeling of the flow-loaded artery (15). Thus, MMP-induced IEL fenestrations are formed following increased blood flow, contributing to arterial distensibility and resulting in an enhanced arterial diameter. As arterial caliber gradually increases, wall shear stress diminishes and the stimulus for MMP production/activation fades.

In summary, vessels are normally exposed to two types of mechanical forces: (a) circumferential stress acting tangentially on the vascular wall and directly related to pressure and dimensions (diameter and thickness) of the vessel, and (b) shear stress acting in a longitudinal direction at the blood–endothelium interface and directly related to the flow-velocity profile. Significant variations in mechanical forces, of a physiological or physiopathological nature, occur in vivo. These are accompanied by phenotypical modulation of the SMC and the endothelial cells, producing structural modifications of the arterial wall. In all the cases, vascular remodeling can be attributed to a modification of the tensional strain or shear, and underlies a trend to reestablish baseline mechanical conditions.

III. Membrane Signal Transduction

Vascular cells are equipped with numerous receptors that allow them to detect and respond to the mechanical forces generated by pressure and shear stress. The cytoskeleton and other structural components have an established role in mechanotransduction, being able to transmit and modulate tension within the cell via focal adhesion sites, integrins, cellular junctions, and the extracellular matrix. The cytoskeleton is composed of three major types of protein filaments: microtubules, microfilaments, and intermediate filaments. Microfilaments are polymers of actin that together with a large number of actin-binding and associated proteins form a continuous, dynamic connection between nearly all cellular structures. The cytoskeletal network changes in response to extracellular stimuli and participates in transmembrane signaling, providing a scaffold for organizing or translocating signaling molecules and organelles. Beyond the structural modifications incurred, mechanical forces can thus initiate complex signal transduction cascades leading to functional changes within the cell, often triggered by activation of integrins, but also by stimulation of other structures such as G-protein receptors, tyrosine kinase receptors, or ion channels (Fig. 2).

A. Integrins

The extracellular matrix is an important contributor to the process of mechanotransduction, containing glycoproteins that are displaced by stretch or shear forces and interact with integrins. The latter proteins contribute not only to cell attachment to the substrate, but also to intracellular transmission of mechanical signals. Mechanical stresses stimulate conformational activation of cell integrins and increase cell binding to the

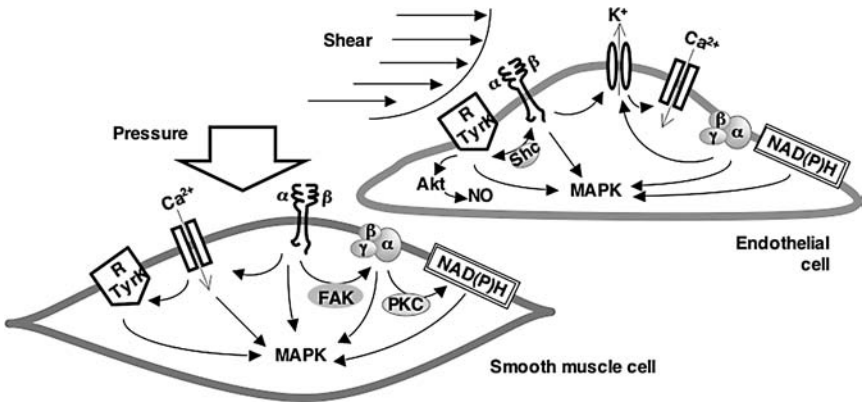

Figure 2 Schematic representation of receptors involved in initiating signaling cascades in vascular cells stimulated by pressure (stretch) or shear stress.

extracellular matrix (16). In fact, the dynamic formation of new integrin–ligand connections is required for stretch- or shear-induced mechanotransduction, because blocking unoccupied extracellular matrix ligand sites with isotype specific antibodies or RGD peptides (RGD being the principal amino acid sequence on extracellular matrix proteins to which integrins bind) inhibits intracellular signaling induced by mechanical forces (16,17). The cytoplasmic domain of integrins is functionally linked to various intracellular proteins that constitute the cytoskeleton and numerous kinases such as focal adhesion kinase (FAK), a key regulator of biochemical cascades initiated by mechanical forces. Integrins therefore form a signaling interface between the extracellular matrix and the cell.

Integrins exist as $\alpha\beta$ pairings that interact with extracellular matrix components including fibronectin (ligand for $\alpha5\beta1$ and $\alpha v\beta3$), vitronectin (ligand for $\alpha v\beta3$), and laminin (ligand for $\alpha6\beta1$). The capacity of cells to sense mechanical forces and the ensuing responses therefore depend on specific integrin–extracellular matrix interactions. For example, cyclic stretching of SMC grown on fibronectin or vitronectin induces cellular proliferation, which is prevented by anti-$\beta5$ or anti-$\alpha v\beta3$ antibodies, whereas SMC grown on elastin or laminin do not proliferate under the same conditions (17). In comparison, cyclic stretch induces greater expression of the SM-1 isoform of myosin heavy chain in SMC plated on laminin than in SMC grown on on collagen or fibronectin (18). Finally, in SMC plated on type I collagen, serum induces the expression of c-*fos* and cell proliferation in stretched cells and unstretched controls equally. However, in SMC grown on elastin matrix, both the serum-induced expression of c-*fos* and the ensuing cell proliferation are abated by stretch (19).

Shear stress also induces integrin-specific signaling cascades. In endothelial cells plated on fibronectin or vitronectin, but not on collagen or laminin, shear triggers $\alpha v\beta3$-dependent mechanotransduction and association of the integrin with the adapter protein Shc. In contrast, shear stress causes association of $\alpha6\beta1$ with Shc in cells plated on laminin, but not on fibronectin, vitronectin, or collagen (16). In cultured endothelial cells, shear stress activates the nuclear factor NFκB, which, acting as the shear stress response element, can promote the expression of mechanosensitive genes. Incubating endothelial cells with an anti-$\alpha v\beta3$ antibody prevents the activation of NFκB by shear stress (20). Perhaps most importantly, in isolated coronary arteries, where endothelial cells lie on native extracellular matrix, flow-dependent dilation can be abrogated by addition of RGD peptides to the culture medium (21). Similar results are obtained when anti-$\beta3$ antibodies are used (21).

Integrins are therefore key sensing elements involved in mechanotransduction in vascular cells. The nature of the mechanical stimulus and the substrate components to which the cells are attached determine which integrin–ligand pairs will be recruited and which downstream intracellular

cascades will be activated, and hence the ensuing cell response. In this context, whole vessel preparations are particularly adapted to the study of the role of integrins in mechanotransduction, because cells are then in their original three-dimensional and complex extracellular matrix environment.

B. Ion Channels

Two different mechanosensitive channels have been described in vascular cells: shear-activated potassium channels and stretch-activated channels (22). Stretch-activated ionic channels are cation-specific and have an electric activity mainly detectable at the time of their opening. The activation of these channels leads to calcium (Ca^{2+}) influx followed by membrane depolarization (22). A role for stretch-activated cation channels in mechanotransduction in SMC was confirmed using the specific blocker gadolinium (23). Flow-induced smooth muscle marker protein expression was reduced by gadolinium, whereas other calcium channel blockers, such as verapamil, did not inhibit the stimulatory effect of shear. Gadolinium also prevents cell proliferation observed in periodically stretched SMC (24).

Exposing endothelial cells in culture to shear stress leads to membrane hyperpolarization due to potassium channel opening (25). Because calcium entry in the cell is dependent on membrane potential, the increase in this potential induced by shear raises Ca^{2+} intake, resulting in an accumulation of calcium in endothelial cells and an enhancement of calcium-dependent signaling cascades. This interpretation is supported by experiments showing on the one hand that endothelial cells do not possess voltage-dependent calcium channels, and on the other hand that high extracellular potassium concentrations reduce calcium entry into these cells (25). Recently, upregulation and activation of endothelial intermediate-conductance Ca^{2+}-activated K^+ channels [IK(Ca)] was reported in endothelial cells exposed to laminar shear stress (26).

Nevertheless, the mechanisms involved in the control of open/closed ion channel conformations by shear remain obscure. One likely contributor is the cytoskeleton, which by deformation could alter channel activation state. In support of this hypothesis, one study implicates cytoskeleton–G-protein coupling in shear-induced potassium channel opening (27). Another recent work highlights a direct role for gadolinium-sensitive channels in endothelial endothelin-1 expression stimulated by rotating integrin-linking RGD peptide–covered ferromagnetic beads (28), establishing a functional link between integrins, the cytoskeleton, and ion channels. As shown by Davies (29), in areas where flow is alternately laminar and turbulent and where mechanical forces vary within short distances, shear and stretch can induce synergistic or antagonistic effects through differential activation of ion channels. Ultimately, the physiological role of various ion channels, sensitive either to shear stress or to stretch, appears to depend on the balance between these hemodynamic forces in the circulation.

C. Heterodimeric G Proteins

G proteins consist of three subunits, α, β, and γ, which couple membrane receptors with intracellular signaling cascades. If one considers the crucial role of G proteins in the regulation of the cardiovascular system, it is not surprising to find that they participate in the transduction of mechanical forces in the endothelium. Indeed, it has been shown that shear-induced regulation of platelet-derived growth factor (PDGF) gene expression is regulated by a protein kinase C (PKC)-dependent mechanism requiring the presence of calcium and G-protein induction (30). The same authors also reported that shear induces the expression of c-*fos* via a complex mechanotransduction cascade involving PKC, phospholipase C, G proteins, and calcium (31). Moreover, the direct effect of shear on the activation of Gαq/α11 and Gαi3/αo in endothelial cells was demonstrated (32), and the activation of both these G proteins was found to be necessary for the activation of downstream signaling cascades (33).

The γ subunit of heterodimeric G proteins is reported to be present at integrin-rich focal adhesion sites and adjacent to F-actin filaments stress fibers (34). Colocalization of G proteins and integrins would even allow for a single signal to activate two transmembrane receptor families simultaneously, G protein–coupled receptors and integrins. Thus, G proteins could be indirectly involved in integrin-mediated signaling. Indeed, G protein inhibition prevents activation of potassium channels stimulated by cell adhesion to the extracellular matrix via integrins (35). Acting on integrins, shear deforms the cytoskeleton and so activates a G protein that opens the potassium channels. Interestingly, there are thus far no indications that mechanical forces can activate G proteins in vascular SMC.

D. Receptor Tyrosine Kinases

Another class of membrane proteins, receptor tyrosine kinases, also take part in mechanotransduction. For example, activation and phosphorylation of PDGF receptor-α are observed in SMC exposed to cyclic stretch or shear stress (36). That could be explained by a disturbance of the cellular surface or an alteration of the receptor conformation by mechanical forces (36). However, the participation of gadolinium-sensitive Ca^{2+} channels cannot be excluded. Indeed, the latter are implicated in the phosphorylation of the EGF receptor by mechanical stimulation (37). The role of the phosphorylation of EGF receptors in mechanotransduction was highlighted when protein synthesis induced in stretched SMC was blocked when the cells were incubated with an EGF receptor antagonist (37).

In endothelial cells, shear stress induces the transitory phosphorylation of the VEGF receptor Flk-1 and its association with Shc and αvβ3 and β1 integrins (38). If the role of Flk-1 in mechanotransduction has not yet been perfectly established, it remains that preventing the association

of Shc with Flk-1, or with other proteins, attenuates the downstream activation cascades as well as the gene transcription stimulated by shear (38).

E. Oxygen-Free Radicals

Recent data suggest that oxygen-free radicals, as well as endogenous antioxidants, probably have critical signaling functions in cells (39). A significant source of vascular oxygen-free radicals is the membrane oxidase NADH/NADPH, whose activity is controlled by hormones, growth factors, and mechanical forces. The basic product of this enzymatic system is the superoxide anion (O_2^-), which is transformed quickly into H_2O_2 by superoxide dismutase. The H_2O_2 is transformed in its turn by two enzymes, catalase and glutathione peroxidase. The breakdown products of the H_2O_2, including lipid hydroperoxides, are also biologically active. On the whole, oxygen-free radicals thus comprise several potential secondary messengers.

The production of oxygen-free radicals has been detected in endothelial cells exposed to a cyclic stretch of 10% to 12% (40), and similarly, applying a 10% cyclic stretch to human coronary artery SMC stimulates the production of O_2^-, while a stretch of 6% does not have any significant effect (41). The activation of PKC, which is induced by stretch and which can activate NADPH oxidase, could in certain cases precede the generation of O_2^- (41). However, 10% cyclic stretch stimulates generation of O_2^- and downstream signaling independently of PKC in whole vessel preparations (42). It has also been proposed that an increase in H_2O_2 in endothelial cells can induce the reorganization of F-actin, characterized by the formation of stress fibers and the recruitment of vinculin to focal adhesion sites (43). Furthermore, the endothelial oxidative response to stretch is matrix protein–dependent, and is reduced by coincubation with RGD peptides or blocking antibodies to $\alpha 2$- and β-integrin antibodies (44).

Interestingly, NADH oxidase activity is upregulated in endothelial cells exposed to oscillatory shear for 24 hours, whereas steady laminar shear induces a more transient response (45). In fact, at 24 hours, steady shear induces superoxide dismutase, unlike oscillatory shear (45), consistent with the atheroprotective quality of laminar flow.

IV. Intracellular Signal Transduction

A. NO and Akt

One of the early events that occurs in endothelial cells placed under flow is the activation of the endothelial NO synthase (eNOS) and the subsequent release of NO. Recent studies show that the activation of eNOS by shear stress does not require Ca^{2+} influx in the cell, as is the case for its activation by vasoactive agonists, but rather its phosphorylation by Akt (or protein kinase B) (46), which is itself phosphorylated by phosphatidylinositol-3-kinase (47).

The intracellular transduction pathways that link shear with eNOS activation are numerous. On the one hand, eNOS activation by shear can be prevented by a potassium channel blocker and necessitates an intact cytoskeleton. On the other hand, the phosphorylation of eNOS and of Akt in endothelial cells under flow is sensitive to tyrosine kinase inhibitors, indicating a possible implication of receptors for VEGF or insulin (48). Akt activation is also observed in cultured SMC subjected to a cyclic stretch (49).

In addition to its role of vasodilator, NO intervenes in the regulation of the vascular remodeling induced by chronic shear stress, because inhibition of this pathway attenuates the increase in diameter observed in arteriovenous fistulas and thus prevents flow-dependent adaptation (2). As a result, the vessel loses its capacity for enlargement and shear levels stay at an abnormally high level. Under this condition, NO plays the role of cofactor, facilitating metalloproteinase activation (15). In addition, Akt activation and the production of NO support the survival of the vascular cells by stimulating antiapoptotic pathways and inhibiting proapoptotic cascades (47).

B. Focal Adhesion Kinase

During the stimulation of vascular cells by mechanical factors such as stretch or shear, several signaling events are associated with the formation of focal adhesions, which comprise integrin clusters and cytoskeletal proteins, as well as various tyrosine kinases, including FAK. There are in fact several different proteins that are known to bind the cytoplasmic domain of integrins, and which may also be involved in mechanotransduction. Nevertheless, the role of FAK is particularly well established in the context of mechanotransduction. Indeed, a recent study shows that FAK is activated in stretched pulmonary vessels, in particular in the endothelium (50), and activation of this enzyme was also demonstrated in cultured endothelial cells exposed to shear stress (51). The recruitment of integrins to focal adhesion sites is mediated by their cytoplasmic domains, which bind proteins of the cytoskeleton (52). The proteins present at focal adhesions become phosphorylated on tyrosine when the cells are stimulated, and FAK activation is an indicator in focal adhesion formation, rather than the engine of their assembly (53). c-Src, a tyrosine kinase associated with the membrane, also plays a role in the process of FAK activation. Following its activation by stretch, c-Src is transferred to the focal contacts (54), where it interacts with an autophosphorylation site on FAK and creates an acceptor for the Src-homology-2 domain of Grb2 and thus supports association of FAK with the latter (Fig. 3). Although not shown yet in the context of mechanotransduction, activation of FAK could also involve RhoA, because inhibition of this small G protein by *Clostridium botulinum* C3 exoenzyme transferase disassembles focal adhesions and reduces phosphorylation of FAK in endothelial cells (55) and VSMCs (56).

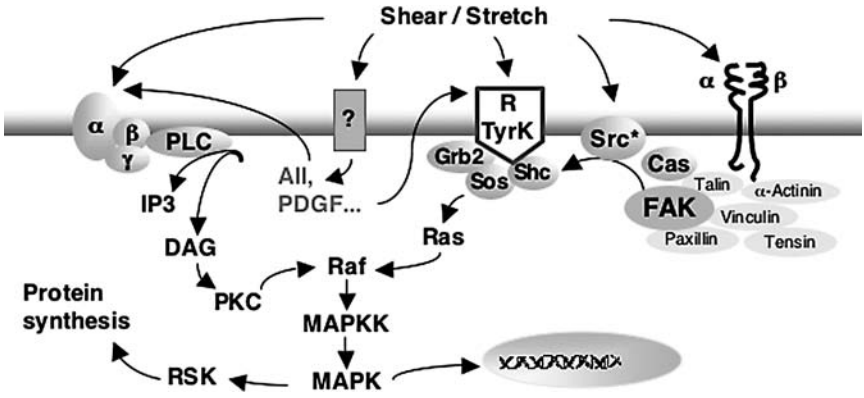

Figure 3 Diverse pathways potentially involved in the activation of MAP kinases (ERK1/2 in this diagram) by mechanical factors. *Abbreviations*: MAP kinases, mitogen-activated protein kinases; ERK, extracellular signal-regulated kinase.

C. The Mitogen-Activated Protein Kinase Cascade

The mitogen-activated protein (MAP) kinase cascade is an important pathway whereby signals originating from mechanical forces can lead to gene expression and protein synthesis (57). This pathway implicates the sequential phosphorylation and activation of the cytoplasmic protein kinases MAP kinase kinase kinase (MEKK), map kinase kinase (MEK), and finally MAP kinase. The MAP kinase cascade comprises in reality three different pathways that are triggered in response to various stimuli and initiate distinct cellular responses. The phosphorylation of one of the MAP kinases, which lies downstream of Raf and is present under two isoforms, ERK1 and 2 (extracellular signal-regulated kinase), leads to the activation of regulatory proteins in the cytoplasm and the nucleus. Other MAP kinases, called stress-activated protein kinases because they are activated by stimuli such as ultraviolet light, heat shock, hypoxia, or hyperosmolarity, include C-jun N-terminal kinases (JNK) (which phosphorylate the amino-terminal of the transcription factor c-jun), and p38.

There is ample evidence that MAP kinases are activated in vascular cells exposed to mechanical forces, both in vivo and in vitro. Cyclic stretch activates ERK1/2 and JNK in cultured SMC (58), and ERK1/2 and JNK are transiently activated in the arterial wall by acute hypertension (59). Using aortic segments in organ culture, it was shown that high intraluminal pressure (150 mmHg) induces a biphasic stimulation of ERK1/2, characterized by an acute activation peak with return to baseline at two hours, and a second, more prolonged rise within 24 hours and lasting at least three days (60). A similar phenomenon, though slower in its acute phase, was also observed in vessels exposed to 10% cyclic stretch (42). In the latter model,

cyclic stretch also activated p38 (42). Finally, MAP kinase activation pathways were also underscored in endothelial cells, in which shear forces of 12 dyne/cm^2 induced the phosphorylation of ERK1/2 and p38, but reduced the activity of JNK (61).

The activation of MAP kinases most likely involves integrins as upstream mechanical sensors for several reasons. First, the in vitro response of vascular cells to stretch or shear varies considerably according to the nature of the substrate on which the cells are plated. For example, both ERK1/2 and JNK are activated by cyclic stretch in neonatal SMC grown on pronectine, but if the same cells are grown on laminin, only JNK is stimulated by cyclic stretch (58). Second, in endothelial cells, ERK1/2 activation by shear or following adhesion to fibronectin occurs via a common integrin-dependent pathway sensitive to the c-Src kinase family inhibitor herbimycin A and dependent on PKC (62). Third, overexpression of FAK increases fibronectin-dependent c-Src kinase activity and subsequent activation of ERK2, whereas a dominant negative Ras blocks activation of ERK1/2 without affecting phosphorylation of FAK or c-Src activity (54). Finally, substitution of the c-Src acceptor on FAK blocks the transmission of signals between integrins and ERK1/2 (54). Taken together, these observations highlight a pathway starting with integrin activation, focal adhesion assembly, FAK activation by c-Src, association with Grb2 driving c-Src-dependent activation of Ras, and ultimately activation of ERK1/2 via the MAP kinase cascade (Fig. 2).

Pathways other than the ones described above also participate in mechanotransduction. For instance, there is evidence that integrin-dependent activation of MAP kinases can in certain cases bypass FAK. Adhesion to matrix can activate ERK in cells expressing a mutant form of the β1 integrin lacking the cytoplasmic segment necessary for FAK interaction (63). Furthermore, the MAP kinase cascade can also be activated by tyrosine phosphorylation of α, β, and γ GTP subunits of G proteins (64), as well as by mechanosensitive phosphorylation of tyrosine kinase type receptors (36–38). As described above, cyclic stretch induces the release of oxygen-free radicals in cultured cells. The activation of Ras by oxygen-free radicals, which in theory precedes activation of Raf and the MAP kinase cascade, was reported (65), in agreement with the observed activation of ERK1/2 by O_2^- in SMC (66). Finally, the inhibition of small G protein RhoA or its downstream kinase, RhoA kinase (p160ROCK), completely prevents stretch-induced ERK1/2 activation (67) or shear-induced JNK activation (68).

Not surprisingly, different pathways can bridge the gap between mechanical stimulation and ERK1/2 activation in vascular cells. As an example, both high intraluminal pressure (150 mmHg) and 10% cyclic stretch activate ERK1/2 in vessels in organ culture. Nonetheless, c-Src kinase inhibition prevents ERK1/2 activation only in vessels at high pressure, and not in pulsatile vessels. On the other hand, activation of ERK1/2 by cyclic stretch is

mediated by the release of oxygen-free radicals (42,60). In comparison, shear-induced ERK1/2 activation in cultured endothelial cells is prevented by inhibition or downregulation of PKC, or inhibition of tyrosine kinase activity, and is probably coupled with the activation of G proteins (69). Hence multiple MAP kinase activation pathways can be induced by stretch or shear in vessels, depending on the nature of the mechanical stimulus and the cell types and the extracellular matrix environment involved.

The events that occur downstream of the activation of MAP kinases are numerous and varied. Once phosphorylated, ERK1/2 can transfer to the nucleus, where it interacts with and phosphorylates transcription factors, thus controlling gene expression. Both ERK1/2 and JNK can lead to ternary complex formation with the serum response element, present on several gene promoters, and thus increase transcriptional activity (70). Alternatively, phosphorylation of the protein PHAS-I (phosphorylated heat- and acid-stable protein), a translation regulation factor, supports the dissociation of the PHAS-I–eukaryotic initiation factor (eIF) -4E complex, normally closely apposed when PHAS-I is relatively underphosphorylated, releasing eIF-4E, which in turn initiates translation in the nucleus (71). Another downstream target of ERK1/2 in SMC is the 90-kDa ribosomal S6 kinase, which, by activation of the transfer RNA–binding factor, provides an additional pathway for initiation of translation (71). Finally, ERK1/2 activation leads to enhanced expression of c-*fos* and c-jun and to activation of the AP-1 transcription factor, and as such is likely to play a significant role in the regulation of cell cycle progression and in protein synthesis in SMC (71). The availability of downstream ligands could be a factor that determines the biological response to ERK1/2 activation.

V. Conclusion

Blood vessels have autocrine and paracrine hormonal mechanisms that enable them to react immediately to local hemodynamic modifications involving tangential mechanical stretch (which increases with pressure) or shear stress (which increases with blood flow). Vascular tone is modified almost immediately to compensate for changes in the environment, and in most cases, this efficiently restores mechanical forces to normal levels. Exceptionally, the variations in vasomotor tone are not sufficient to compensate for the new mechanical constraints, and the phenotype of the vascular cells is altered, causing local modifications in trophicity. At length (over a few days to a few weeks), these adaptative changes also tend to return mechanical forces to their physiological values. Vascular remodeling is observed in various situations where the local pressures and flows are modified, such as arterial hypertension, atherosclerosis, arteriovenous fistula, stenosis, and aneurysm.

Many receptors, present on the surface of endothelial cells and SMC, allow vessels to detect subtle changes in their physical environment. From that point, different mechanotransduction cascades can be initiated according to the nature of the mechanical stimulus perceived. Inside the vascular cells, cytoskeletal proteins transmit and modulate the tension between focal adhesion sites, integrins, and the extracellular matrix. In addition to the structural modifications induced by the mechanical forces, they may lead to changes in the ionic composition of the cells, mediated by ion channels, stimulate various membrane receptors, and induce complex biochemical cascades. Many intracellular pathways, such as the MAP kinase cascade, are activated by flow or stretch and initiate, via sequential phosphorylations, the activation of transcription factors and subsequent gene expression. Thus, by purely local mechanisms, the blood vessels are capable of a true autonomic regulation, which enables them to adapt to their mechanical environment.

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2

Pulmonary Micromechanics of Injured Lungs

ROLF D. HUBMAYR

Division of Pulmonary and Critical Care Medicine, Mayo Clinic
Rochester, Minnesota, U.S.A.

I. Introduction

Many controversies about mechanical ventilation–associated injury mechanisms can be traced to uncertainties about the small-scale stress and strain distributions in healthy and diseased lungs. It seems, therefore, prudent to begin by discussing the physical determinants of regional lung volume and ventilation in healthy lungs and only then consider the effects of injury on regional mechanics within this framework. I consider it important to detail certain principles in solid mechanics that are applicable to lung biology, not because the principles are new, but because they are fundamental for dealing with the topic at hand. The reader who wishes to go beyond my brief description of these principles is referred to specific chapters in the *Handbook of Physiology* (1–3). Finally, I note that some of my arguments about the distribution of edema in injured lungs, which of course has bearing on alveolar mechanics, have been summarized in a previously published opinion piece (4).

II. Determinants of Regional Pressure and Volume in Health and Disease

The lung is a tissue network that offers relatively little resistance to shape change. Therefore, when it became known in the middle of the 20th century that there are vertical gradients in regional lung expansion and pleural pressure, it made perfect sense to liken the lungs to a liquid. That analogy generated a number of testable hypotheses: (i) the vertical gradients in pressure and volume are determined by the average density of the lung; (ii) changes in body posture have no effect on the magnitude of the gravitational volume and pressure gradients. Physiologists soon realized that measurements of pleural pressure and regional lung volume in experimental animals were not consistent with these predictions and, therefore, they considered alternative mechanisms. Specifically, observed vertical pressure and volume gradients failed to scale with lung density, and most importantly, the gradients changed substantially with body posture (5–8). Because the critical care community at that time had not yet appreciated the relevance of regional lung function for the ventilator management of critically ill patients, clinicians did not pay much attention to what seemed to be an esoteric debate.

Because the lungs did not behave like a liquid, physiologists began to approach questions about the in situ topographical distribution of pressure and volume as a shape-matching problem between two gravitationally deformed elastic solids: the lungs and the chest wall (2). Figure 1 helps to appreciate this concept. The stress and strain distributions of a cone-shaped sponge that is forced to completely fill a rigid cylinder are shown. Gravity is only relevant insofar as it is a determinant of the shape of the cone before it is forced to assume the cylindrical shape. A useful way to think about the lung/thorax shape mismatch is to imagine what shapes the lungs and chest wall would assume before they are forced to conform to each other. The considerable displacement of the diaphragm–abdomen with posture certainly underscores the importance of gravity on the shape of the chest wall. If, by chance gravity deformed the lungs in exactly the same way, then the lungs would be uniformly expanded in the chest and exposed to exactly the same surface pressure (pleural pressure) everywhere. Because that is not the case (at least in large animals and humans in the supine or upright posture), the topographical distribution of pressure and volume must reflect the size of the shape mismatch and the resistance of either structure to a shape change. In material science, this resistance is referred to as shear modulus. It is distinct from other measures of elastic properties such as compliance or bulk modulus, but related to it. In the case of liquids, this resistance is zero. In the case of solids, it may be considerable. Case in point: the hydrostatic pressure gradient in a water glass does not care about the shape of the glass, yet it is difficult to fit a square peg into a round hole.

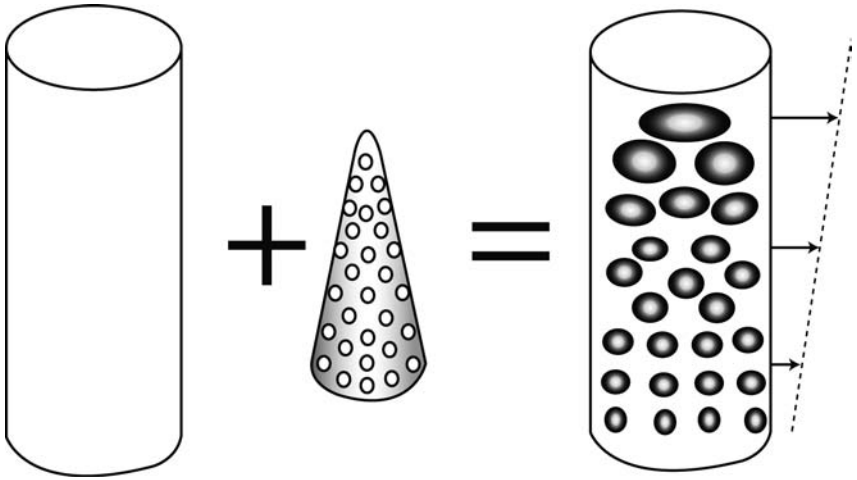

Figure 1 The diagram shows a very simple, but nevertheless instructive shape-matching problem (the fitting of an elastic cone into a rigid cylinder). As long as the elastic solid (the cone) resists a shape change (behaves like a solid rather than a liquid), its stress distribution will be shape dependent. Note that the vertical orientation of the stress and strain gradients need not imply a gravitational mechanism. For example, the experiment shown here might well have been conducted in a gravity-free environment. *Source*: From Ref. 4.

Once these principles were understood, it became clear that the weight of the lung could only be one (possibly minor) determinant of a lung/thorax shape mismatch (9,10). Lung weight will determine by how much the lungs will slump (deform) when they are taken out of the chest and by how much the dependent alveoli are compressed when the lungs are supported on a hard surface. However, until one knows by how much this "compressed" lung must deform to fit into the gravitationally deformed thorax, it is impossible to predict the in situ stress (pressure) and strain (volume) distributions. These principles hold true in health as well as in disease. What makes disease more difficult to deal with is the greatly increased small-scale heterogeneity in mechanical properties (such as local shear moduli), which contribute greatly to local stress distributions (see discussion on interdependence).

Experiments on normal animals conducted in the 1970s and 1980s established that the lung weight accounts for no more than 20% of the vertical gradient in pleural pressure and alveolar volume (6,7,11). In other words, under normal conditions, the lung weight is only a minor determinant of the topographical distribution of parenchymal stress and strain. In contrast, the weights of the abdomen and heart greatly influence the gradients in intrathoracic pressure and volume (7,11,12). Both heart and

diaphragm/abdomen are lung boundary structures and as such their gravitational deformations define the shape the lungs must deform to. Proof of concept was provided by Bar-Yishay et al., who filled the heart of upright canine cadavers with mercury and showed a dramatic effect on pleural pressure gradients (12). One of the first observations, which raised concerns about the weight of the lung hypothesis, was the lack of a vertical pressure or volume gradient in prone animals. One attractive explanation is the difference in heart position and support between the two postures (13). As shown in Figure 2, in the prone posture, the heart rests on the sternum, whereas in the supine posture, the weight of the heart is balanced by pleural pressure in the mid-chest. During a change from the prone to the supine posture, the heart "sinks" from the sternum toward the spine. As it does so, the lungs enter the substernal space vacated by the heart. The resulting lung deformation and the associated local stress generate a "suction pressure" (negative pleural pressure) that prevents the heart from coming to rest entirely on the spine. In other words, the weight of the heart is an important source of the vertical pleural pressure gradient in supine animals (and

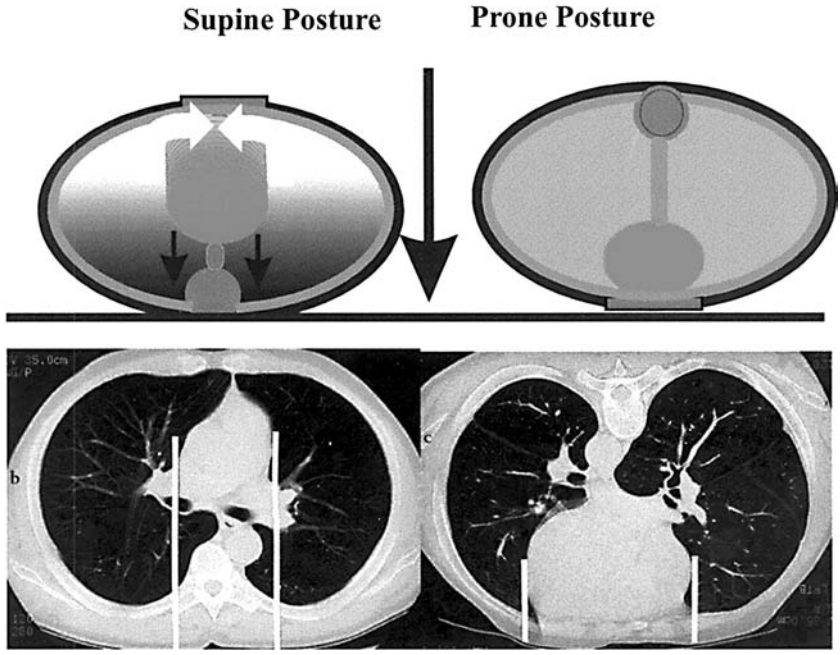

Figure 2 Schematic (*upper panel*) and CT images of volunteers (*lower panel*) illustrating the effects of posture on the position of the heart relative to lungs and thorax. *Abbreviation*: CT, computed tomography. *Source*: From Ref. 13.

presumably humans), and it is thought to contribute to the "proning" related recruitment of the dorsal units of injured lungs (13–15).

The "weight of the lung hypothesis" reemerged after computer tomography (CT) images of patients with acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) showed preferential consolidation of the dependent diaphragm near lung regions (16–21). Dependent atelectases were attributed to compression of the dorsal lung by the increased weight of the edematous superimposed tissue. While it is certainly possible that fluid that invariably accumulates in injured lungs accentuates a mechanism that normally is insignificant, several arguments were brought forth that challenged the superimposed pressure idea (4). Measurements of tissue dimensions (as opposed to regional air content) in oleic acid–injured dogs failed to demonstrate vertical gradients in regional lung expansion (22). In these studies the regional lung volume was defined as the sum of tissue, blood, edema fluid, and air. The most plausible interpretation of the data was that following injury alveolar air was simply replaced by alveolar fluid. As a result the dimensions of alveolar walls and the local stress (transmural pressure) on them need not change appreciably even though the pleural pressure over dependent lung could have increased dramatically. That is because alveolar pressure in dependent fluid or foam-filled acini no longer equals the pressure at the airway opening. Once one accepts that most forms of lung injury impair the vascular barrier properties, then the images of edematous lungs published by Bachofen and Weibel in the early 1990s serve as a powerful reminder of the small-scale heterogeneity in interfacial tension and hence of mechanical properties (23,24).

Because the determinants of the lung parenchymal stress and strain distributions in the intact thorax depend critically on the lungs' resistance to a shape change, the effects of injury on lung mechanical properties becomes an important variable. It is not my intent to review the considerable literature on the pressure–volume (PV) curve of patients with injured lungs, because Chapter 6 deals with this topic in considerable detail. Moreover, the information obtained from the whole lung PV measurements is insufficient to characterize the apparent shear modulus of the injured lung. What can be concluded is that an injured lung is less deformable than a normal lung. Several candidate mechanisms exist that readily explain the greater shear modulus of injured lungs. These include interfacial tensions associated with airway closure by liquid bridges and foam, solidification (gel formation) of alveolar exudate, increased surface tension and the consequently increased prestress of the axial elastin and collagen fiber network (see below under the sections "Micromechanics of the Normal Lung" and "Alveolar Micromechanics in Injury States"), interstitial edema and matrix remodeling, and finally scar formation and fibrosis. In light of the injury effect on the deformation resistance of the lung parenchyma, it cannot be a priori assumed that the greater lung weight is responsible for the consolidation of dependent lung.

III. Micromechanics of the Normal Lung

For more than 50 years, it has been appreciated that the topographical distributions of lung parenchymal stress and strain are nonuniform and, as just outlined, the biophysical determinants of this nonuniformity are generally understood. However, with increasing precision in the methods for measuring regional lung function, it is now apparent that there is considerable small-scale heterogeneity in lung parenchymal strain, which cannot be explained by any gravitational mechanism (11,25).

The lung parenchyma is a tissue network that is distorted by surface tension (Fig. 3) (26,27). Embedded in this network are airways and blood vessels, whose resistance to deformation exceeds that of the parenchyma by varying degrees. In the late 1970s, Bachofen, Weibel, and coworkers

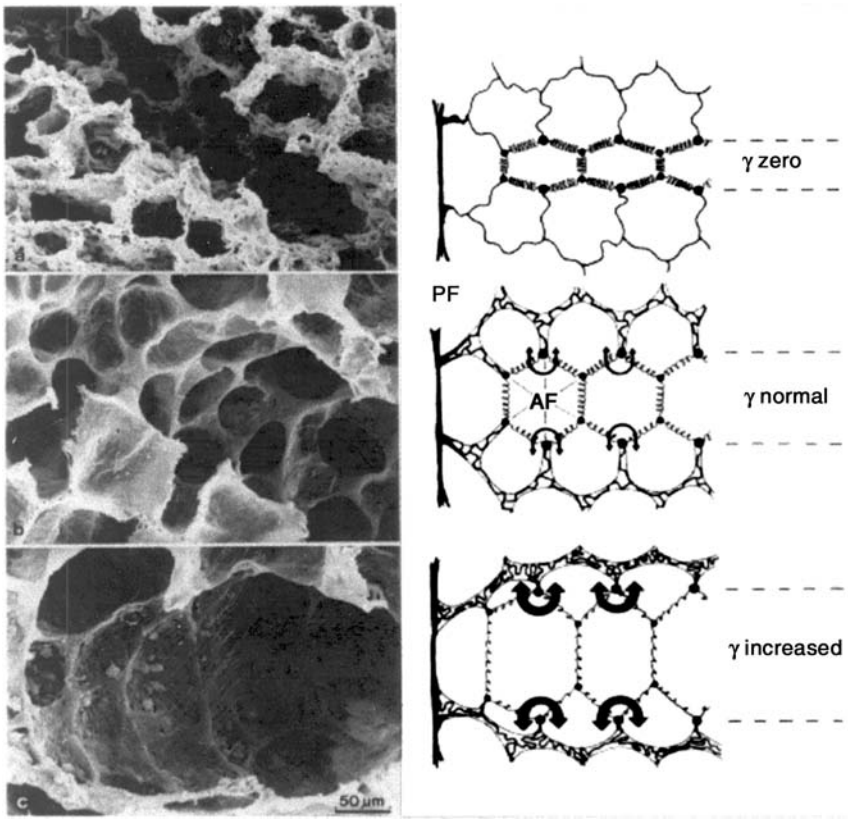

Figure 3 Scanning electron micrograph of an alveolar duct and adjacent alveoli and the schematic of pulmonary micromechanics demonstrate the effects of surface tension on acinar stress/strain distributions. *Source*: From Ref. 26.

reported on the morphology of rabbit lungs at different lung volumes and for different values of surface tension (28–30). These studies identified three components of the tissue structure of the lung. One is the peripheral tissue system that includes the pleural membrane and membranes that penetrate the lung and connect to sheaths that surround the airways. This is a self-contained system that is extended as lung volume increases, but is unaffected by surface tension. It provides the only contribution to recoil in the saline-filled lung, and its contribution to recoil in the air-filled lung is the same as to the recoil of the saline-filled lung. The second component of the tissue structure is the axial system, namely a helical network of elastin and collagen fibers that extend from the terminal conducting airways to form alveolar ducts and the line elements at the alveolar openings (31–34). This second tissue component is tensed by surface tension, i.e., surface tension generates prestress in the axial fiber system. The third component of the tissue structure is the fine fibrils of connective tissue that thread through the alveolar walls. This component is assumed to be unstressed except at high lung volumes.

Guided by Weibel's description of the architecture of the lung, the qualitative appearance of the micrographs, and the quantitative data, Wilson and Bachofen (35) constructed a model for the mechanical properties of the acinus. The model alveolar duct consisted of intersecting helical elastic line elements that defined the lumen of the duct and formed the free edges of alveolar walls that extended outward from the helical line elements. The alveolar walls were assumed to carry no tissue stress and to serve only as platforms for surface tension at the air–liquid interface. Tension and length of the line elements were determined by a balance between the hoop stress in the line and surface tension on the alveolar walls. As a consequence, the dimensions of alveolar ducts increase with increasing surface tension, at the expense of alveolar surface area (Fig. 3). Because alveolar walls are the planes along which surface tension acts, any increase in surface tension will also promote tissue buckling at alveolar corners.

It should be acknowledged that not all investigators subscribe to the Wilson–Bachofen views of acinar micromechanics. Some view alveoli as a scaffold that simply supports surfactant foam (36), while others have entertained the notion that the alveolar liquid lining could be discontinuous so that surfactant interacts directly with plasma membranes and with "local puddles" of an aqueous subphase (37). Finally, some think that alveoli exist in only one of two states, i.e., expanded and recruited or collapsed and derecruited (38). Indirect support for this hypothesis arises from movies of subpleural lung units of mechanically ventilated animals (39,40). These movies failed to reveal appreciable changes in the alveolar projection images during breathing. Considering the technical challenges and assumptions upon which the different schools of thought base their arguments, the mechanisms by which the lungs change volume remain controversial.

The time-honored method of making detailed morphometric measurements of perfusion-fixed lung tissues has been plagued by uncertainty about artifacts from tissue desiccation and preservation (41). Nevertheless, the derived data clearly form the basis of mainstream thinking (42). Intravital microscopy on the other hand has limited three-dimensional (3-D) resolution and is restricted to alveoli that are anchored to the pleural membrane. Because the pleural membrane area change must scale with the tidal volume to the 2/3 power (43), it is hard to imagine that alveoli, which are anchored to that membrane, would be able to resist expansion in the plane of the membrane. Yet, no such expansion was demonstrated with intravital microscopy (39). This raises the question of an experimental setup that requires that the pleura be brought into apposition to a coverslip by gentle suction and as a result constrains local deformation.

The data on lung morphology and the model of acinar micromechanics provide a number of insights and predictions that are relevant for understanding mechanical ventilation–related injury mechanisms. Over much of the lungs' volume range, the parenchyma simply unfolds as opposed to getting stretched (27,44,45). In other words, the parenchyma and, specifically, the alveoli behave more like wrinkled cellophane bags than deflated rubber balloons. Consequently, the stress acting on cells and on the tissue matrix of alveolar walls is small and more or less constant up to lung volumes of 70% total lung capacity (TLC). Tschumperlin and Margulies traced the lengths of alveolar basement membranes in electron microscopic images of rat lungs and estimated their area change with transpulmonary pressure and volume. Accordingly, the basement membrane area increased by approximately 35% during an inspiratory capacity maneuver, which corresponds to a linear strain of approximately 15% (45). Importantly, the stress–strain (transpulmonary pressure–basement membrane area) relationship was highly nonlinear and suggested that elastic tissue deformation occurred only at high volumes.

As will be discussed below, these insights have a bearing on the interpretation of PV curves of injured lungs. One of the "hallmarks" of injury is a rightward shift of the lung PV curve. Because surface tension, as one important determinant of lung recoil, has a very nonlinear effect on alveolar wall stress and strain, a rightward shift of the lungs' PV curve due to surfactant inactivation need not have any bearing on the probability of deformation injury from tissue failure. Consider a sphere of tissue that is coated with an air–liquid interface. A change in surface tension will alter the pressure required to preserve the volume of the sphere, but this will have no effect whatsoever on the tissue stress itself. Indeed, the Wilson–Bachofen model argues that increases in surface tension unload alveolar walls, while shifting the acinar PV curve to the right (26,35). Until one integrates topographical heterogeneity in surfactant function, in airspace edema, and in local impedance into models of alveolar mechanics, it should be appreciated that a rightward shift of the lung PV curve by itself does not inform

about tissue stress and about the probability of tissue stress failure or "biotrauma" from mechanical ventilation.

IV. Alveolar Micromechanics in Injury States

Injured lungs possess two attributes that explain why they are at an increased risk for deformation injury. The first attribute is that the number of airspaces capable of expanding during inspiration is decreased, an attribute referred to by Gattinoni et al. as "baby lung" (18). Unless tidal volume is reduced in proportion, units that do expand during breathing are exposed to a greater deforming stress. This explains the increased risk of injury from regional overexpansion. The second attribute is that the local impedance to lung expansion is heterogeneous because of the heterogenous distributions of the liquid and the surface tension in distal airspaces. This heterogeneity in lung impedances results in shear stress being generated between neighboring, interdependent units that operate at different volumes (46). The stability of a fluid layer on the wall of an airway has been analyzed (47). The results show that if enough fluid to form a liquid bridge across the airway is available, the bridge will form. However, estimates of the magnitude of the pressure difference that could be supported by foam or liquid bridges in the airways are not available.

Figure 4 shows subpleural alveoli of two isolated perfused rat lungs that had been imaged with laser confocal microscopy (4). The image on the left is a 3-D representation of a normal lung. The image on the right is a single optical slice $\approx$30 μm below the pleural surface of an injured lung that had been perfused with a solution containing fluorescein-labeled dextran. Edema fluid appears white, the alveolar walls gray, and trapped air black. Note that the alveolar walls of the edematous lung are wavy, that the alveoli are completely or partially flooded, and that they contain air pockets of different sizes and shapes. The observations are reminiscent of those by Bachofen et al. based on electron micrographs of edematous rabbit lungs (23,24). The presence of different sized air pockets with different radii of curvature implies a nonuniform alveolar gas pressure and/or nonuniform surface tensions. Regional differences in the physicochemical properties of the surfactant as suggested by Bachofen et al. could well be the source of the nonuniform surface tension. Maintenance of a nonuniform alveolar gas pressure raises the possibility that the air pockets are trapped by liquid and foam in conducting airways. It opens the possibility that crackles, which are readily heard in edematous lungs, are generated by the collapse of unstable bubbles as opposed to the explosive expansion of a previously collapsed alveolus. In either case, the image conveys the impression that the mechanical impedance to lung inflation is heterogenous both within and between small neighboring structures.

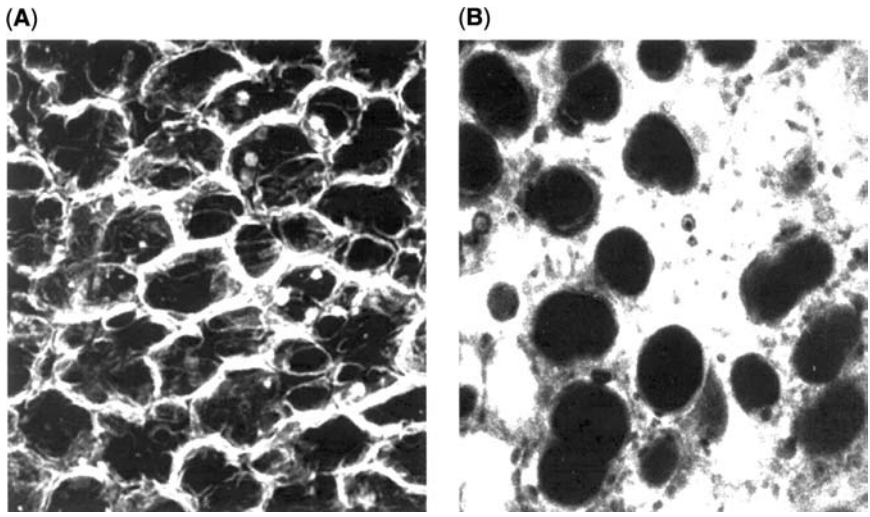

Figure 4 Laser confocal micrograph of subpleural airspaces of a normal (**A**) and an edematous (**B**) rat lung. Edema fluid contains fluorescein-labeled dextran and appears white. For discussion of mechanisms, refer to text. *Source*: From Ref. 4.

The most convincing examples of heterogenous lung expansion in injury states have been provided by the team of Nieman, who recorded the volume expansions of subpleural alveoli during mechanical ventilation in different injury models (48–50). In contrast to the normal lung in which the apical regions of subpleural alveoli appeared uniformly expanded, injury states were associated with greatly nonuniform alveolar expansions. Because it is difficult to distinguish between the tissue and edema fluid by light microscopy, the images convey the cyclic appearance and disappearance of gas bubbles at the apices of subpleural alveoli. While this observation is insufficient for characterizing the mechanisms of alveolar recruitment and derecruitment as tissue opening and collapse, it nevertheless does underscore the tremendous heterogeneity in local mechanics. This has an obvious bearing on interdependence as a risk factor for deformation injury in edematous lungs. As anticipated, the application of positive end-expiratory pressure (PEEP) increased the number of aerated subpleural alveoli and restored alveolar mechanics toward normal (49).

Wilson et al. modeled the micromechanics of the edematous alveolus and tested the validity of the model assumptions against measurements of regional lung expansion in oleic acid-injured dogs (51). The model depicted in Figure 5 was adapted from the classic Wilson–Bachofen model, which had successfully described the dependence of lung recoil and surface area on lung volume and surface tension (35). In that model, the line elements

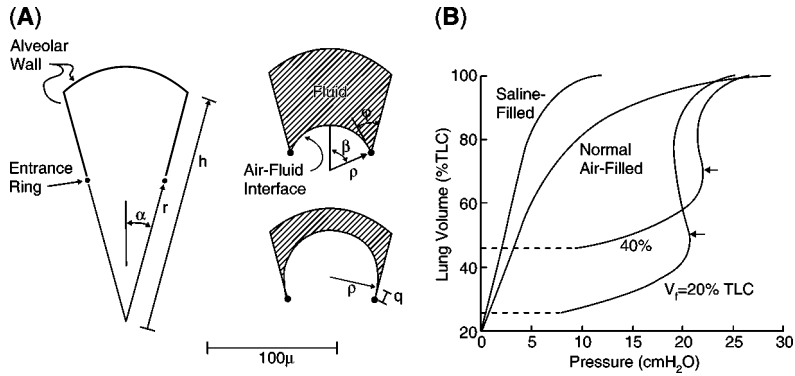

Figure 5 Model of edematous alveolus (**A**) and corresponding prediction of the pressure/volume behavior of the edematous lung (**B**). For discussion of mechanisms, refer to text. *Source*: From Ref. 51.

at the alveolar openings were pictured as helices. Alveolar walls extended radially outward from the helices, but the geometry of the alveolus was not specified. In the case of alveolar edema, Wilson modified that model by describing the alveolar geometry in detail. This detail was required in order to add fluid to the model. By modeling the side walls of the alveolus as a cone, the geometry of the fluid pool and the air–liquid interface could be described simply. However, this model was not as self-consistent as the earlier model. In particular, it was not possible to match a model alveolus with cylindrical symmetry around a vertical axis to a duct with cylindrical symmetry around a horizontal axis.

The edema model retains the crucial elements of the original model, namely, the dimensions of the outer boundary of the duct depend on lung volume alone. Tension and length of the line element at the inner boundary are determined by a balance between the hoop stress and surface tension. Surface area is a function of both the outer and inner dimensions and depends on lung volume as well as surface tension. In the model for edema, the fluid in the lung was assumed to be confined to the interior of the alveolus. This assumption is consistent with the micrographs of edematous lungs presented by Bachofen et al. (23,24). In these micrographs, the alveolar ducts and alveolar mouths are open, and the alveolar walls are separate and distinct. With smaller amounts of edema fluid, the fluid is confined to the interior corners of the alveoli. With larger amounts of fluid, the fluid pools extend to the free edges of the alveolar walls, and the air–liquid interfaces are smoothly curved.

In the edema model, at the lowest lung volume, fluid fills the alveolus, and the tangent to the air–liquid interface is orthogonal to the entrance

ring. As a result, the ring is slack and does not contribute to recoil. As lung volume increases, the fluid retreats into the alveolus, the angle between the tangent to the air–liquid interface and the alveolar wall (phi in Fig. 5) decreases, the entrance ring expands, and pressure rises rapidly because of the rapid increase in tension in the entrance ring. Above the volume at which the air bubble is enclosed in the alveolus (phi = 0), tension in the ring is independent of volume and the PV curve is nearly vertical as it is for lungs that have been rinsed with a liquid with high surface tension (52–54). Thus, the model generates a PV curve with a low compliance at low volumes, a pronounced knee, and high compliance at higher volumes. The shape of the curve is like the shape of the PV curves of edematous lungs (51,55), but the explanation for this shape is quite different from that based on the hypothesis that alveoli or airways are in the collapsed state at low volumes and pop open at a critical pressure.

V. Mechanisms by Which Ventilators Injure Lungs

Once the critical care community appreciated that mechanical ventilation could damage the lungs in more ways than "barotraumas," as defined by Macklin and Macklin some 60 years ago (56), literally hundreds of experimental studies were conducted with the aim of establishing cause and effect relationships between specific ventilator settings and some biologic responses (57). In aggregate, these studies have established four specific ventilator-induced lung injury (VILI) mechanisms: (a) regional over distension (58–60) caused by the application of a local stress or pressure that forces cells and tissues to assume shapes and dimensions that they do not assume during unassisted breathing; (b) so-called "low volume injury" (61,62) associated with the repeated recruitment and derecruitment of unstable lung units, which causes the abrasion of the epithelial airspace lining by interfacial forces; (c) the inactivation of surfactant (63,64) triggered by large alveolar surface area oscillations that stress surfactant adsorption and desorption kinetics and are associated with surfactant aggregate conversion; and (d) interdependence mechanisms (46) that raise cell and tissue stress between neighboring structures with differing mechanical properties.

A. Overdistension Injury

When airspaces are exposed to high luminal pressures, the resulting deformation of the connective tissue matrix is transmitted to endothelial and epithelial cells that line the capillary basement membrane. The deformed cells may lose contact with the matrix and/or experience yielding (fracture) of their stress-bearing elements, i.e., cytoskeleton and plasma membrane (60).

Consequently cells die and are cleared by macrophages or heal, express stress response genes, and initiate a proinflammatory immune response. Associated changes in vascular permeability promote alveolar flooding, which alters the molecular organization of the surfactant and inhibits its surface tension–lowering activity (65). When the stress is very large, not only cells but also basement membranes fracture, allowing the passage of red blood cells into the alveolar space (66,67). Together these events explain the cardinal clinical manifestations of ventilator-associated lung injury, namely, edema, increased impedance to lung inflation ("stiff lungs"), reduced alveolar gas content, impaired gas exchange, and alveolar hemorrhage, microvascular thrombi, and inflammation (57). The cellular physiology and biomechanics as it pertains to stretch or overexpansion injury is reviewed in Chapter 3.

The probability of overdistension injury is clearly related to the magnitude of the inflation pressure and the corresponding maximal lung volume (59,68). The inspiratory capacity of adults with healthy lungs is several liters. Therefore, it is highly unlikely that even very large machine-delivered tidal volumes would injure normal lungs by an overdistension mechanism. In contrast, diseased lungs are vulnerable to overdistension because fewer lung units are capable of expanding during inspiration. Gattinoni et al. coined the term "baby-lung" to highlight this determinant of deformation risk (17,18). Because it is difficult to measure thoracic gas volume in critically ill patients, most experts accept a plateau pressure of $\geq$30 cmH_2O as a surrogate threshold of lung stress that produces overdistension. This threshold was, in fact, chosen by the investigators of the ARDSnet low tidal volume trial, which established the efficacy of lung-protective mechanical ventilation (69).

End-inspiratory hold or plateau pressure (P_{plat}) is the elastic recoil pressure of the relaxed respiratory system at end-inflation. In normal individuals, the recoil pressure of the chest wall near TLC approximates 10 cmH_2O, so that a P_{plat} of 30 cmH_2O corresponds to a lung stress (i.e., lung elastic recoil pressure) of approximately 20 cmH_2O. The stiffness (elastic modulus) of normal lungs increases at distending pressures above 20 cmH_2O. Many clinicians refer to the part of the inflation PV curve at which stiffness begins to increase as the upper inflection point and consider the corresponding deformation as one at which the lungs approach their structural limit. While the reasons for relating injury to lung volume, distending pressure, and the shape of the respiratory PV curve are compelling, the evidence in support of a single numeric threshold remains at best circumstantial.

As already pointed out, in injury states, the determinants of lung recoil are exceedingly complex and only peripherally related to alveolar wall stress. Consistent with the effects of disease on the inspiratory capacity, in patients with ALI, the tidal volume that generates a P_{plat} above the upper

inflection point may be indeed quite small (70). Yet most experimental and clinical studies have failed to convincingly uncouple overdistension from other injury mechanisms, so that the debate whether tidal volume injures lungs independent of P_{plat} remains unsettled (57,69,71,72). Moreover, patients' chest wall mechanical properties are quite variable, and it should not be assumed that P_{plat} -10 cmH_2O (i.e., normal chest wall recoil) equals lung stress (73). This is particularly true in recumbent patients with ascites, ileus, or morbid obesity (74,75). In many of them plateau pressures between 35 and 40 cmH_2O may not only be safe, but actually desired (refer to Chapters 6, 7, and 20). Some experts advocate the placement of esophageal balloon catheters to directly estimate pleural pressure (P_{pl}), and thus chest wall compliance. However, esophageal manometry is invasive and subject to artifacts, and although measurements of P_{pl} have been reported in critically ill patients, the technique cannot be considered validated in this population (73,76,77). In injured lungs, the topographical distribution of alveolar and pleural pressure is nonuniform. Therefore, there is no guarantee that the measured pressure reflects the weighted average of all pressures acting on the chest wall. Quite to the contrary, there is every reason to think that in supine patients, the end-inspiratory transpulmonary pressure, defined as the difference between airway and esophageal pressure, is severely biased (underestimated) due to the weight of the mediastinum on the lower esophagus (4,72,76).

Recent analyses of CT images of patients with ALI suggested that injured lungs may be overdistended at $P_{plat} \leq 30$ cmH_2O (78). Overdistension was inferred from the frequency distributions of pixel Houndsfield units (HU), which are measures of the local gas to liquid (essentially water) ratios. At TLC, a normal lung contains 10% water (tissue plus blood) per unit gas volume. Provided that pixels are sufficiently large relative to the scale of the microstructure, pixels with a tissue to gas ratio $<10\%$ (corresponding to HU ≤ -900) would have had to originate from structures that contained more air than a normal lung at TLC. By definition, this means that these units were overexpanded, or had a local blood content smaller than that of a normal lung at TLC. Such an occurrence is to be anticipated in patients with bullous emphysema or barotrauma, but the observation is somewhat surprising in the context of noncardiogenic pulmonary edema from ALI (79). In fact, the investigators report that some regions met CT criteria for overinflation even at functional residual capacity and many regions did so at a PEEP level of 15 cmH_2O. This amount of PEEP would not be expected to distend normal lung structures to TLC, unless local surface tension was extremely low. The most plausible explanation for the findings is a remodeling and stress adaptation of lung structures that had been preferentially deformed during mechanical ventilation prior to imaging. In the sample of patients who were studied, lesions were primarily observed in the substernal diaphragm-apposed regions of the lung.

B. Low Volume Injury

There is strong experimental evidence that PEEP protects the lungs from mechanical injury (61,68,80–83). The responsible mechanism is thought to be the PEEP-mediated increase in volume and elastic recoil, which prevents the repeated opening and closing of the otherwise unstable lung units. At least early in the progression of ALI, unstable units tend to be located in dorsal paraspinal regions of the lungs (16,17). The reasons why dorsal regions appear most susceptible to atelectasis (lack of aeration) can be traced to normal physiology. In the supine posture, dependent regions of the normal lung empty close to their residual volume, undergo large tidal expansions during inspiration, and receive most of the pulmonary blood flow (1,11,84). Therefore, insults to the capillary integrity of the lungs are likely to promote alveolar flooding, closure of airspaces by liquid plugs, surfactant inactivation, and gas absorption atelectasis in this part of the lungs.

The injury mechanism associated with the repeated opening and closure of dependent airspaces may be attributed to interfacial forces that are generated by the respiratory movement of air–liquid interfaces across their epithelial lining. Such forces may be generated during the rupture of a liquid microfilm that separates the apposing epithelial lining cells of a truly collapsed airspace that is pried open. A similar injury mechanism may be envisioned during the to and fro movement of a liquid or foam plug in an airway with normal dimensions. Modeling approaches to bubble and liquid flow in tubes, while constrained by simplifying assumptions (e.g., rigid tube of uniform diameter, smooth surface, etc.) are beginning to shed some light on the more quantitative aspects of this problem (62,85–88). In experimental systems, these forces are large enough to damage cell membranes and may be reduced by the application of surfactants. Because Chapter 7 is devoted to the biomechanical basis of low volume injury, it will not be reviewed in detail here.

PEEP protects the injured lungs by decreasing the probability of liquid bridge formation in small airways. It does so by increasing the space in which lung water may be distributed. While increasing airspace dimensions, PEEP also promotes the translocation of fluid from alveoli into the interstitial space (89). Occlusion of an airway by a liquid bridge promotes gas absorption and flooding behind the occlusion. The resulting deformation of the effected tissue, often referred to as atelectasis or collapse, is in large part determined by local alveolar–capillary barrier properties. If the vasculature is leaky and alveolar fluid absorption impaired, then liquid will simply replace alveolar gas and the original tissue dimensions will remain preserved. However, if local barrier properties are normal, then the subtended region will decrease in size and the stress at its boundary will increase as predicted by interdependence mechanisms (see section on "The Importance of Interdependence as an Injury Mechanism"). In either case, the

diffusion distance will have increased between the inspired gas and the capillary blood, and gas exchange will be impaired. But the consequences for local microstrains and immune mechanisms ("biotrauma"), which are in part determined by the local concentrations of bioactive molecules, could be profoundly different in the two scenarios. While there are no data that clearly speak to this issue, it is self-evident that PEEP or a change in posture will be less effective in "opening" a "closed" airspace once the liquid exudates transform into gel in the later stages of lung injury syndromes (90).

C. Effects of Tidal Volume on Surfactant Kinetics and Function

Surfactant is a lipid–protein mixture, which lowers alveolar surface tension, and thereby stabilizes peripheral lung units (the reader is referred to Chapter 26). Structure, molecular composition, and biophysical properties of pulmonary surfactants are profoundly altered in injured lungs (64,91,92). Moreover, mechanical ventilation is apt to stress surfactant kinetics, and thereby contribute to a depletion of bioactive surfactant (93). Because alveolar surface area increases during inspiration, surfactant lipids are adsorbed to the air–liquid interface and are organized there by surfactant proteins. The decrease in alveolar surface area during expiration results in buckling of the lipid film and the squeeze-out of surfactant material into the liquid subphase. With each adsorption/squeeze-out cycle some molecules lose function and need to be replenished by newly secreted lamellar bodies. In a sense, breathing "consumes" bioactive surfactants and the rate of consumption is directly proportional to the amplitude of surface area oscillations, i.e., local tidal volume. The loss of function is reflected in an increase in the small aggregate surfactant subfraction (64,65). The small aggregate subfraction contains very little protein and many small unilamellar vesicles, which are incapable of lowering surface tension.

These mechanisms of surfactant inactivation have obvious bearing on the debate if one may relax tidal volume restrictions in patients with injured lungs, as long as peak and plateau airway pressures are considered to be in the "safe" range. Safe means that inflation pressures are below levels at which normal lungs are expanded close to their TLC, which most proponents of this approach place near 30 cmH_2O. Implicit in this argument is the belief that lung tissue overdistension is the prevailing deformation injury mechanism, while hyperventilation-associated surfactant inactivation is not. Two observations raise caution against this belief. First, it is possible to injure the lungs of experimental animals by pharmacologic induction of spontaneous hyperventilation (94). More importantly, a secondary analysis of ARDS clinical trials network data, which had established the efficacy of lung protective mechanical ventilation, demonstrated a survival benefit from tidal volume reductions even in the subgroup of patients with the lowest plateau airway pressures (Chapter 20).

D. The Importance of Interdependence as an Injury Mechanism

The interconnectedness between elements of a network such as the lung parenchyma promotes uniform expansion of individual units. When a unit, be it an alveolus, a lobule, or a lung segment, resists expansion because the airway that supplies it with gas is obstructed, the neighboring units exert a large inflationary stress on it. This is because stress, by definition, increases when the sum of forces of the surrounding tissue attachments act over a smaller than expected surface area. Moreover, the tension and strain of individual connective tissue elements that insert into the collapsed segment increase out of proportion to those of the more remote network structures. Strain (fractional length change) of a tissue element that attaches to a lung unit resisting deformation decays exponentially from the point of insertion. The relevance of interdependence on lung biology was first recognized by Mead et al., who used a simple balloon network to illustrate its cardinal features (46). They showed that to empty a single balloon that is a part of a balloon network, a suction pressure several-fold greater than the average inflation pressure had to be applied. Even though Mead ignored the strain gradients in surrounding network structures, their estimates of local stress turned out to be quite accurate.

Many observations in lung biology can be traced to interdependence. They include the redistribution of alveolar fluid from the airspace to interstitium in response to PEEP (89) as well as the accumulation of fluid (in the case of edema), red blood cells (in the case of capillary stress failure), and air (in the case of barotrauma) along bronchovascular bundles (95). Large airways, blood vessels, and interstitial connective tissue resist deformation to a greater extent than the surrounding parenchyma. Consequently, lung expansion creates a local tensile stress at the surface of airways, blood vessels, and interstitium, which drives fluid, blood, or air as the case may be toward that space.

VI. Concluding Remarks

As the appreciation for specific injury mechanisms has grown, so has the realization that the lungs' responses to injurious stress can be quite nuanced and nonuniform with respect to space and time. In fact in 1998, Tremblay and Slutsky coined the term "biotrauma" to precisely underscore this point (96). Because it would be naive to assume that the many distinct manifestations of biotrauma contain identical prognostic or mechanistic information, it would seem prudent to differentiate between specific pulmonary stress responses. After all, the term "injury" has been used to describe biologic responses as diverse as altered gene or protein expressions, abnormal respiratory mechanics, inefficient gas exchange, impaired vascular barrier properties, and the remodeling of lung structures.

There is a delicate interplay between physical injury mechanisms, the focus of this chapter, and biotrauma, the biologic response to the injurious stress. This is because many of the lungs' "biotrauma" responses amplify their susceptibility to deformation injury. Markers of "biotrauma" are often used in translational research as surrogate endpoints of treatment effect. However, VILI is a dynamic process, which is hard to capture at a single point in time. Hence, the relative "value" of specific surrogate treatment targets, be they oxygenation, lung aeration, or cytokine concentrations, is likely to change as a function of time as well. In light of this complexity it would be foolish to ignore the many gaps in our knowledge of pulmonary micromechanics. After all we are still debating how a normal lung deforms during a breath.

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