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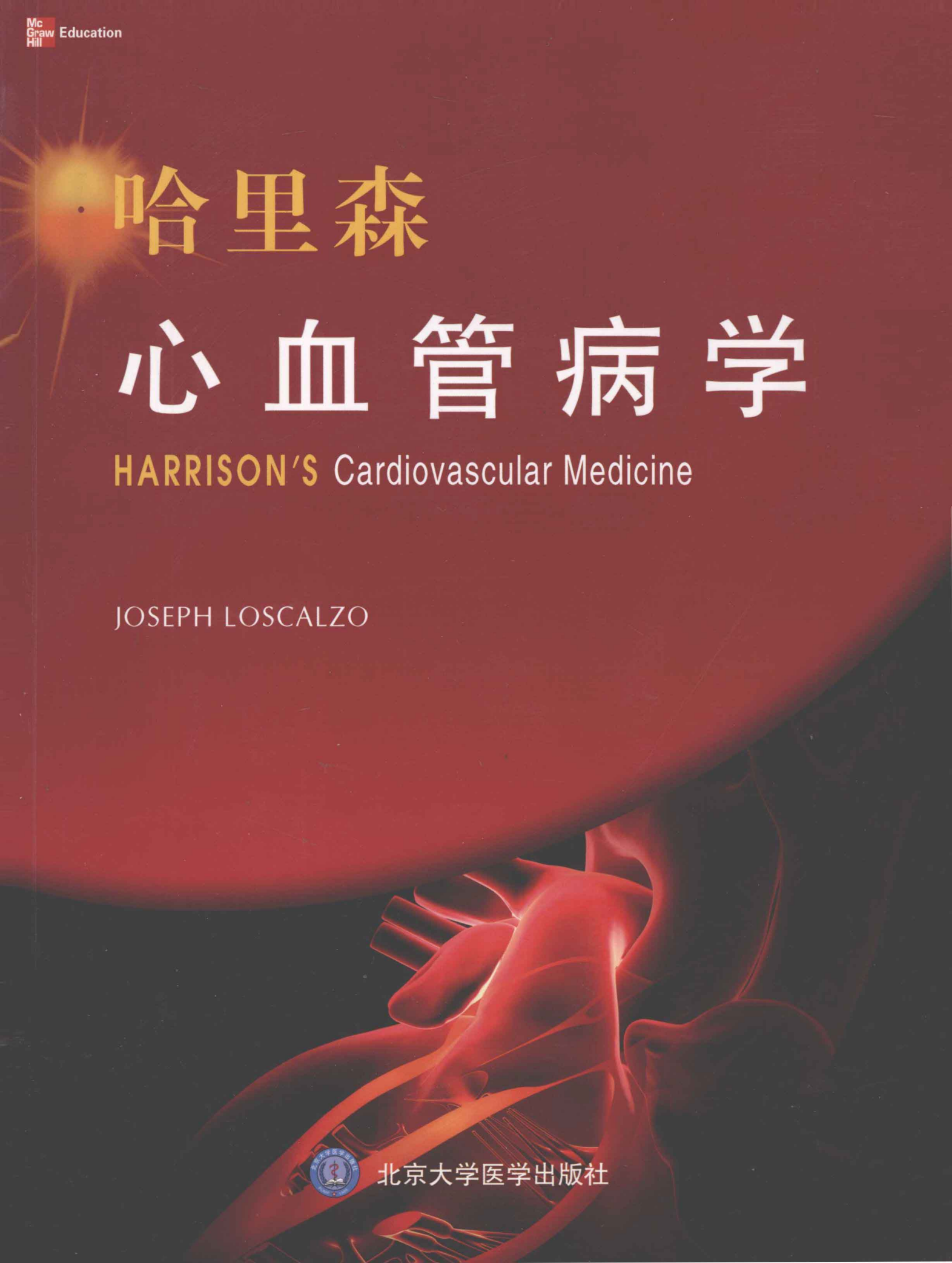
心血管病学

HARRISON'S Cardiovascular Medicine

JOSEPH LOSCALZO



北京大学医学出版社

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Editor

Joseph Loscalzo, MD, PhD

Hersey Professor of Theory and Practice of Medicine,
Harvard Medical School; Chairman, Department of Medicine;
Physician-in-Chief, Brigham and Women's Hospital, Boston

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出版说明

《哈里森内科学》（Harrison's Principles of Internal Medicine）是一部内科学经典名著，也是美国及多个国家医学院校的首选内科学教科书。该书1945年由美国权威内科学家哈里森（Tinsley R. Harrison）首先提议并组织编写，第1版于1950年问世，并立即引起广泛的赞誉与好评。自此，随着医学科学的发展以及在市场的热销，该书每4年修订一次，历时半个多世纪，已出版至第17版，成为内科学发展的基石和风向标，享有“内科学著作之父”的美誉。

为了读者阅读和携带方便，更专注于内科学各亚科领域，《哈里森内科学》分册系列书问世了。该分册系列以《哈里森内科学》（第17版）中相关领域的内容为蓝本，并参考了《哈里森内科学》（第17版）出版以来的最新文献，强调基础与临床的整合，汇集了本领域内最新的进展，是内科学各亚科领域的权威教科书。

在医学领域，英文原版经典专著经过几十年甚至上百年的发展，在知识点的架构上形成了科学而完备的体系，不但语言规范、地道，而且更新及时，具有权威性和先进性。无论是临床医生、教师还是医学生，有这样一本经典专著放在案头，经常翻阅，不但可以获取医学知识，对提高专业外语水平也大有裨益。

本次引进出版：

- 哈里森心血管病学
- 哈里森肾脏病学
- 哈里森临床神经病学
- 哈里森胃肠病学与肝病学
- 哈里森呼吸病学与危重症医学

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CONTRIBUTORS

Numbers in brackets refer to the chapter(s) written or co-written by the contributor.

ELLIOTT M. ANTMAN, MD
Professor of Medicine, Harvard Medical School; Director, Samuel L. Levine Cardiac Unit, and Senior Investigator, TIMI Study Group, Brigham and Women's Hospital, Boston [33, 35]

ERIC H. AWTRY, MD
Assistant Professor of Medicine, Boston University School of Medicine, Boston [23, 24]

DONALD S. BAIM, MD†
Professor of Medicine, Harvard Medical School; Executive Vice President, Chief Medical and Scientific Officer, Boston Scientific Corporation, Natick [13, 36, 44]

GERALD BLOOMFIELD, MD, MPH
Department of Internal Medicine, The Johns Hopkins University School of Medicine, Baltimore [Review and Self-Assessment]

EUGENE BRAUNWALD, MD, MA (Hon), ScD (Hon)
Distinguished Hersey Professor of Medicine, Harvard Medical School; Chairman, TIMI Study Group, Brigham and Women's Hospital, Boston [1, 3, 6, 7, 9, 10, 20, 21, 22, 33, 34, 35]

CYNTHIA D. BROWN, MD
Department of Internal Medicine, The Johns Hopkins University School of Medicine, Baltimore [Review and Self-Assessment]

CHRISTOPHER P. CANNON, MD
Associate Professor of Medicine, Harvard Medical School; Associate Physician, Cardiovascular Division, Senior Investigator, TIMI Study Group, Brigham and Women's Hospital, Boston [34]

JONATHAN R. CARAPETIS, MBBS, PhD
Director, Menzies School of Health Research; Professor, Charles Darwin University, Australia [26]

AGUSTIN CASTELLANOS, MD
Professor of Medicine; Director, Clinical Electrophysiology, University of Miami Miller School of Medicine, Miami [29]

JOHN S. CHILD, MD
Director, Ahmanson-UCLA Adult Congenital Heart Disease Center; Streisand Professor of Medicine and Cardiology, David Geffen School of Medicine at UCLA, Los Angeles [19]

WILSON S. COLUCCI, MD
Thomas J. Ryan Professor of Medicine, Boston University School of Medicine; Chief, Cardiovascular Medicine, Boston University Medical Center, Boston [23, 24]

MARK A. CREAGER, MD
Professor of Medicine, Harvard Medical School; Simon C. Fireman Scholar in Cardiovascular Medicine; Director, Vascular Center, Brigham and Women's Hospital, Boston [38, 39]

ROBERT H. ECKEL, MD
Professor of Medicine, Division of Endocrinology, Metabolism and Diabetes, Division of Cardiology; Professor of Physiology and Biophysics; Charles A. Boettcher II Chair in Atherosclerosis; Program Director, Adult General Clinical Research Center, University of Colorado at Denver and Health Sciences Center; Director Lipid Clinic, University Hospital, Aurora [32]

DANIEL J. FINK,† MD, MPH
Associate Professor of Clinical Pathology, College of Physicians and Surgeons, Columbia University, New York [Appendix]

J. MICHAEL GAZIANO, MD, MPH
Chief, Division of Aging, Brigham and Women's Hospital; Director, Massachusetts Veterans Epidemiology, Research and Information Center (MAVERIC) and Geriatric Research, Education and Clinical Center (GRECC), Boston VA Healthcare System; Associate Professor of Medicine, Harvard Medical School, Boston [2]

THOMAS A. GAZIANO, MD, MSc
Instructor in Medicine, Harvard Medical School; Associate Physician of Cardiovascular Medicine, Brigham and Women's Hospital, Boston [2]

RAYMOND J. GIBBONS, MD
Arthur M. and Gladys D. Gray Professor of Medicine, Mayo Clinic College of Medicine; Consultant, Cardiovascular Diseases, Mayo Clinic, Rochester [12, 42]

JAMES F. GLOCKNER, MD
Assistant Professor of Radiology, Mayo Clinic College of Medicine, Rochester [12, 42]

ARY L. GOLDBERGER, MD
Professor of Medicine, Harvard Medical School; Associate Director, Division of Interdisciplinary Medicine and Biotechnology, Beth Israel Deaconess Medical Center, Boston [11, 41, 43]

HELEN H. HOBBS, MD
Investigator, Howard Hughes Medical Institute; Professor of Internal Medicine and Molecular Genetics, University of Texas Southwestern Medical Center, Dallas [31]

JUDITH S. HOCHMAN, MD
Harold Synder Family Professor of Cardiology; Clinical Chief, the Leon H. Charney Division of Cardiology; New York University School of Medicine; Director, Cardiovascular Clinical Research, New York [28]

SHARON A. HUNT, MD
Professor, Cardiovascular Medicine, Stanford University, Palo Alto [18]

DAVID H. INGBAR, MD
Professor of Medicine, Physiology & Pediatrics; Director, Pulmonary, Allergy, Critical Care & Sleep Division; Executive Director, Center for Lung Science & Health, University of Minnesota School of Medicine; Co-Director, Medical ICU & Respiratory Care, University of Minnesota Medical Center, Fairview [28]

ADOLF W. KARCHMER, MD
Professor of Medicine, Harvard Medical School, Boston [25]

LOUIS V. KIRCHHOFF, MD, MPH
Professor, Departments of Internal Mediciene and Epidemiology, University of Iowa; Staff Physician, Department of Veterans Affairs Medical Center, Iowa City [27]

†Deceased

THEODORE A. KOTCHEN, MD
Associate Dean for Clinical Research; Director, General Clinical Research Center, Medical College of Wisconsin, Wisconsin [37]

ALEXANDER KRATZ, MD, PhD, MPH
Assistant Professor of Clinical Pathology, Columbia University College of Physicians and Surgeons; Associate Director, Core Laboratory, Columbia University Medical Center, New York-Presbyterian Hospital; Director, Allen Pavilion Laboratory, New York [Appendix]

THOMAS H. LEE, MD
Professor of Medicine, Harvard Medical School; Chief Executive Officer, Partners Community Health Care, Inc; Network President, Partners Health Care, Boston [4]

PETER LIBBY, MD
Mallinckrodt Professor of Medicine, Harvard Medical School; Chief, Cardiovascular Medicine, Brigham and Women's Hospital, Boston [1, 30]

JOSEPH LOSCALZO, MD, PhD, MA (Hon)
Hersey Professor of the Theory and Practice of Medicine, Harvard Medical School; Chairman, Department of Medicine, Physician-in-Chief, Brigham and Women's Hospital, Boston [1, 7, 8, 33, 38, 39]

DOUGLAS L. MANN, MD
Professor of Medicine, Molecular Physiology and Biophysics; Chief, Section of Cardiology, Baylor College of Medicine, St. Luke's Episcopal Hospital and Texas Heart Institute, Houston [17]

FRANCIS MARCHLINSKI, MD
Professor of Medicine; Director of Cardiac Electrophysiology, University of Pennsylvania Health System, University of Pennsylvania School of Medicine, Philadelphia [16]

ROBERT J. MYERBERG, MD
Professor of Medicine and Physiology; AHA Chair in Cardiovascular Research, University of Miami Miller School of Medicine, Miami [29]

RICK A. NISHIMURA, MD
Judd and Mary Morris Leighton Professor of Cardiovascular Diseases; Professor of Medicine, Mayo Clinic College of Medicine, Rochester [12, 42]

PATRICK T. O'GARA, MD
Associate Professor of Medicine, Harvard Medical School; Director, Clinical Cardiology, Brigham and Women's Hospital, Boston [10, 20]

ROBERT A. O'ROURKE, MD
Distinguished Professor of Medicine Emeritus, University of Texas Health Science Center, San Antonio [9]

MICHAEL A. PESCE, PhD
Clinical Professor of Pathology, Columbia University College of Physicians and Surgeons; Director of Specialty Laboratory, New York Presbyterian Hospital, Columbia University Medical Center, New York [Appendix]

DANIEL J. RADER, MD
Cooper-McClure Professor of Medicine, University of Pennsylvania School of Medicine, Philadelphia [31]

STUART RICH, MD
Professor of Medicine, Section of Cardiology, University of Chicago, Chicago [40]

JOSHUA SCHIFFER, MD
Department of Internal Medicine, The Johns Hopkins University School of Medicine, Baltimore [Review and Self-Assessment]

RICHARD M. SCHWARTZSTEIN, MD
Professor of Medicine, Harvard Medical School; Associate Chair, Pulmonary and Critical Care Medicine; Vice-President for Education, Beth Israel Deaconess Medical Center, Boston [5]

ANDREW P. SELWYN, MA, MD
Professor of Medicine, Harvard Medical School, Boston [33]

ADAM SPIVAK, MD
Department of Internal Medicine, The Johns Hopkins University School of Medicine, Baltimore [Review and Self-Assessment]

A. JAMIL TAJIK, MD
Thomas J. Watson, Jr., Professor; Professor of Medicine and Pediatrics; Chairman (Emeritus), Zayed Cardiovascular Center, Mayo Clinic, Rochester, Minnesota; Consultant, Cardiovascular Division, Mayo Clinic, Scottsdale [12, 42]

GORDON F. TOMASELLI, MD
David J. Carver Professor of Medicine, Vice Chairman, Department of Medicine for Research, The Johns Hopkins University, Baltimore [14, 15]

CHARLES WIENER, MD
Professor of Medicine and Physiology; Vice Chair, Department of Medicine; Director, Osler Medical Training Program, The Johns Hopkins University School of Medicine, Baltimore [Review and Self-Assessment]

JOSHUA WYNNE, MD, MBA, MPH
Executive Associate Dean, Professor of Medicine, University of North Dakota School of Medicine and Health Sciences, Grand Forks [21]

PREFACE

Cardiovascular disease is the leading cause of death in the United States, and is rapidly becoming a major cause of death in the developing world. Advances in the therapy and prevention of cardiovascular diseases have clearly improved the lives of patients with these common, potentially devastating disorders; yet, the disease prevalence and the risk factor burden for disease (especially obesity in the United States and smoking worldwide) continue to increase globally. Cardiovascular medicine is, therefore, of crucial importance to the field of internal medicine.

Cardiovascular medicine is a large and growing subspecialty, and comprises a number of specific subfields, including coronary heart disease, congenital heart disease, valvular heart disease, cardiovascular imaging, electrophysiology, and interventional cardiology. Many of these areas involve novel technologies that facilitate diagnosis and therapy. The highly specialized nature of these disciplines within cardiology and the increasing specialization of cardiologists argue for the importance of a broad view of cardiovascular medicine by the internist in helping to guide the patient through illness and the decisions that arise in the course of its treatment.

The scientific underpinnings of cardiovascular medicine have also been evolving rapidly. The molecular pathogenesis and genetic basis for many diseases are now known and, with this knowledge, diagnostics and therapeutics are becoming increasingly individualized. Cardiovascular diseases are largely complex phenotypes, and this structural and physiological complexity recapitulates the complex molecular and genetic systems that underlie it. As knowledge about these complex systems expands, the opportunity for identifying unique therapeutic targets increases, holding great promise for definitive interventions in the future. Regenerative medicine is another area of cardiovascular medicine that is rapidly achieving translation. Recognition that the adult human heart can repair itself, albeit sparingly with typical injury, and that cardiac precursor (stem) cells reside within the myocardium to do this can be expanded, and can be used to repair if not regenerate a normal heart is an exciting advance in the field. These concepts represent a completely novel paradigm that will revolutionize the future of the subspecialty.

In view of the importance of cardiovascular medicine to the field of internal medicine, and the rapidity with which the scientific basis for the discipline is advancing, *Harrison's Cardiovascular Medicine* was developed. The purpose of this sectional is to provide the readers with a succinct overview of the field of cardiovascular medicine. To achieve this goal, *Harrison's Cardiovascular Medicine* comprises the key cardiovascular chapters contained in *Harrison's Principles of Internal Medicine, 17e*, contributed by leading experts in the field. This sectional is designed not only for physicians-in-training on cardiology rotations, but also for practicing clinicians, other health care professionals, and medical students who seek to enrich and update their knowledge of this rapidly changing field. The editors trust that this book will increase both the readers' knowledge of the field, and their appreciation for its importance.

Joseph Loscalzo, MD, PhD

NOTICE

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The authors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the authors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or for the results obtained from use of the information contained in this work. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.

Review and self-assessment questions and answers were taken from Wiener C, Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, Loscalzo J (editors) Bloomfield G, Brown CD, Schiffer J, Spivak A (contributing editors). *Harrison's Principles of Internal Medicine Self-Assessment and Board Review*, 17th ed. New York, McGraw-Hill, 2008, ISBN 978-0-07-149619-3.

The global icons call greater attention to key epidemiologic and clinical differences in the practice of medicine throughout the world.

The genetic icons identify a clinical issue with an explicit genetic relationship.

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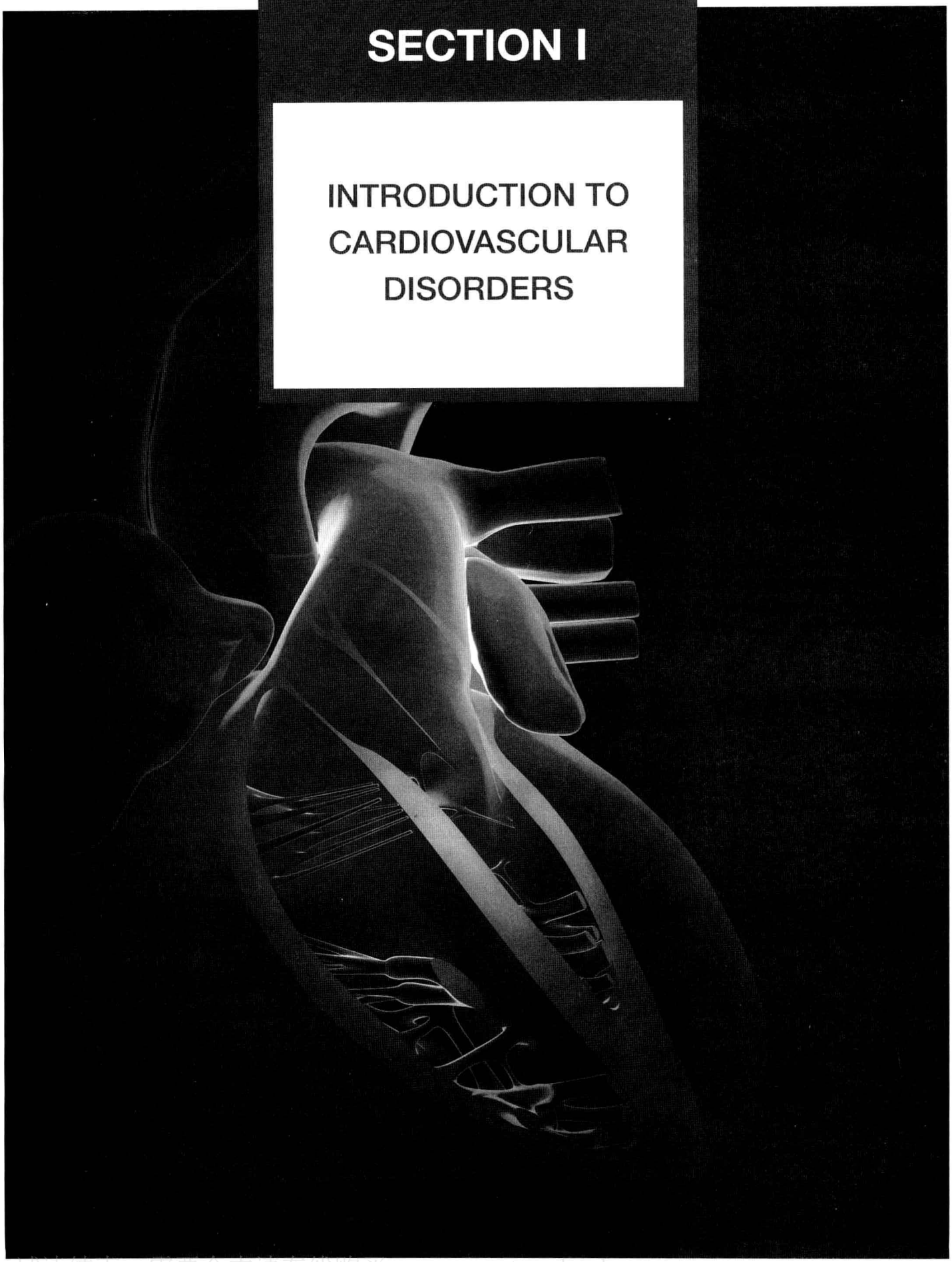
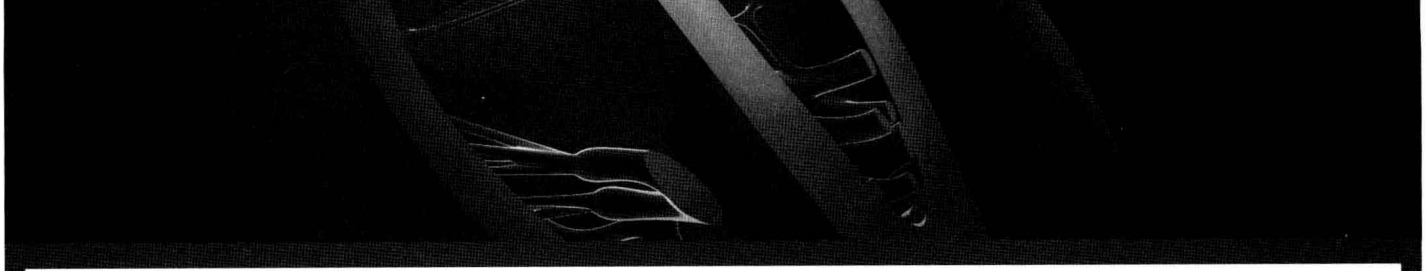
SECTION I

INTRODUCTION TO CARDIOVASCULAR DISORDERS





CHAPTER 1

BASIC BIOLOGY OF THE CARDIOVASCULAR SYSTEM

Joseph Loscalzo ■ Peter Libby ■ Eugene Braunwald

THE BLOOD VESSEL

VASCULAR ULTRASTRUCTURE

Blood vessels participate in homeostasis on a moment-to-moment basis and contribute to the pathophysiology of diseases of virtually every organ system. Hence, an understanding of the fundamentals of vascular biology furnishes a foundation for understanding normal function of all organ systems and many diseases. The smallest blood vessels, capillaries, consist of a monolayer of endothelial cells in close juxtaposition with occasional smooth-muscle–like cells known as *pericytes* (Fig. 1-1*A*). Unlike larger vessels, pericytes do not invest the entire microvessel to form a continuous sheath. Veins and arteries typically have a trilaminar structure (Fig. 1-1*B–E*). The *intima* consists of a monolayer of endothelial cells continuous with those of the capillary trees. The middle layer, or *tunica media*, consists of layers of smooth-muscle cells; in veins, this layer can contain just a few layers of smooth-muscle cells (Fig. 1-1*B*). The outer layer, the *adventitia*, consists of looser extracellular matrix with occasional fibroblasts, mast cells, and nerve terminals. Larger arteries have their own vasculature, the *vasa vasorum*, which nourish the outer aspects of the tunica media. The adventitia of many veins surpasses the intima in thickness.

The tone of muscular arterioles regulates blood pressure and flow through various arterial beds. These smaller arteries have relatively thick tunica media in relation to the adventitia (Fig. 1-1*C*). Medium-size muscular arteries likewise contain a prominent tunica media (Fig. 1-1*D*). Atherosclerosis commonly affects this type of muscular artery. The larger elastic arteries have a much more structured tunica media consisting of concentric bands of smooth-muscle cells interspersed with strata of elastin-rich extracellular matrix sandwiched between continuous layers of smooth-muscle cells (Fig. 1-1*E*). Larger arteries have a clearly demarcated internal elastic lamina that forms the barrier between the intima and media. An external elastic lamina demarcates the media of arteries from the surrounding adventitia.

ORIGIN OF VASCULAR CELLS

The intima in human arteries often contains occasional resident smooth-muscle cells beneath the monolayer of vascular endothelial cells. The embryonic origin of smooth-muscle cells in various types of artery differs. Some upper-body arterial smooth-muscle cells derive from the neural crest, whereas lower-body arteries generally recruit smooth-muscle cells during development from neighboring mesodermal structures, such as the

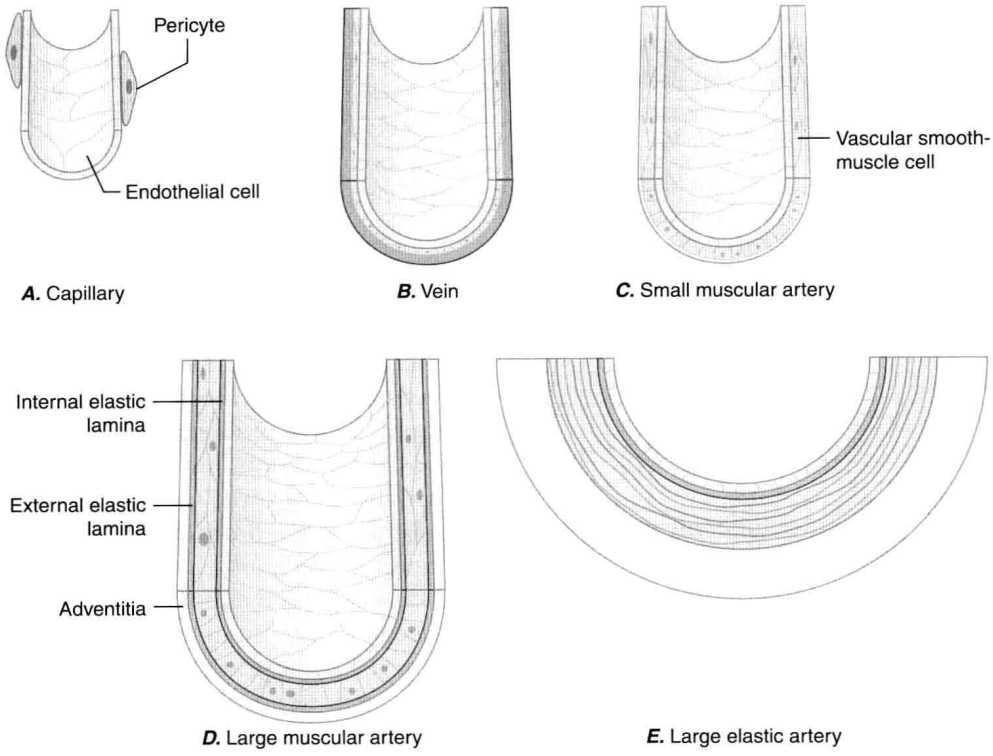


FIGURE 1-1
Schematics of the structures of various types of blood vessels. ***A.*** Capillaries consist of an endothelial tube in contact with a discontinuous population of pericytes. ***B.*** Veins typically have thin medias and thicker adventitias. ***C.*** A small muscular artery consists of a prominent tunica media. ***D.*** Larger muscular arteries have a prominent media with smooth-muscle cells embedded in a complex extracellular matrix. ***E.*** Larger elastic arteries have circular layers of elastic tissue alternating with concentric rings of smooth-muscle cells.

somites. Recent evidence suggests that the bone marrow may give rise to both vascular endothelial cells and smooth-muscle cells, particularly under conditions of repair of injury or vascular lesion formation. Indeed, the ability of bone marrow to repair an injured endothelial monolayer may contribute to maintenance of vascular health and may promote arterial disease when this reparative mechanism fails due to injurious stimuli or age. The precise sources of endothelial and mesenchymal progenitor cells or their stem cell precursors remain the subject of active investigation.

VASCULAR CELL BIOLOGY

Endothelial Cell

The key cell of the vascular intima, the endothelial cell, has manifold functions in health and disease. Most obviously, the endothelium forms the interface between tissues and the blood compartment. It must, therefore, regulate the entry of molecules and cells into tissues in a selective manner. The ability of endothelial cells to serve as a permselective barrier fails in many vascular disorders, including atherosclerosis and hypertension. This dysregulation of permselectivity also occurs in pulmonary edema and other situations of "capillary leak."

The endothelium also participates in the local regulation of blood flow and vascular caliber. Endogenous substances produced by endothelial cells, such as prostacyclin, endothelium-derived hyperpolarizing factor, and nitric oxide (NO), provide tonic vasodilatory stimuli under physiologic conditions in vivo (Table 1-1). Impaired production or excess catabolism of NO impairs this endothelium-dependent vasodilator function and may contribute to excessive vasoconstriction under various pathologic situations. By contrast, endothelial cells also produce potent vasoconstrictor substances such as endothelin in a regulated fashion. Excessive production of reactive oxygen species, such as superoxide anion (O_2^-), by endothelial or smooth-muscle cells under pathologic conditions (e.g., excessive exposure to angiotensin II) can promote local oxidative stress and inactivate NO.

The endothelial monolayer contributes critically to inflammatory processes involved in normal host defenses and pathologic states. The normal endothelium resists prolonged contact with blood leukocytes; however, when activated by bacterial products, such as endotoxin or proinflammatory cytokines released during infection or injury, endothelial cells express an array of leukocyte adhesion molecules that bind various classes of leukocytes. The endothelial cells appear to recruit selectively

TABLE 1-1

ENDOTHELIAL FUNCTIONS IN HEALTH AND DISEASE

HOMEOSTATIC PHENOTYPE	DYSFUNCTIONAL PHENOTYPE
Vasodilatation	Impaired dilatation, vasoconstriction
Antithrombotic, profibrinolytic	Prothrombotic, antifibrinolytic
Anti-inflammatory	Proinflammatory
Antiproliferative	Proproliferative
Antioxidant	Prooxidant

different classes of leukocytes under different pathologic conditions. The gamut of adhesion molecules and chemokines generated during acute bacterial processes tends to recruit granulocytes. In chronic inflammatory diseases, such as tuberculosis or atherosclerosis, endothelial cells express adhesion molecules that favor the recruitment of mononuclear leukocytes that characteristically accumulate in these conditions.

The endothelial monolayer also dynamically regulates thrombosis and hemostasis. NO, in addition to its vasodilatory properties, can limit platelet activation and aggregation. Like NO, prostacyclin produced by endothelial cells under normal conditions not only provides a vasodilatory stimulus but also antagonizes platelet activation and aggregation. Thrombomodulin expressed on the surface of endothelial cells binds thrombin at low concentrations and inhibits coagulation through activation of the protein C pathway, leading to enhanced catabolism of clotting factors Va and VIIIa, thereby combating thrombus formation. The surface of endothelial cells contains heparan sulfate glycosaminoglycans that furnish an endogenous antithrombin coating to the vasculature. Endothelial cells also participate actively in fibrinolysis and its regulation. They express receptors for plasminogen activators and produce tissue-type plasminogen activator. Through local generation of plasmin, the normal endothelial monolayer can promote the lysis of nascent thrombi.

When activated by inflammatory cytokines—bacterial endotoxin, or angiotensin II, for example—endothelial cells can produce substantial quantities of the major inhibitor of fibrinolysis, plasminogen activator inhibitor 1 (PAI-1). Thus, under pathologic circumstances, the endothelial cell may promote local thrombus accumulation rather than combat it. Inflammatory stimuli also induce the expression of the potent procoagulant tissue factor, a contributor to disseminated intravascular coagulation in sepsis.

Endothelial cells also participate in the pathophysiology of a number of immune-mediated diseases. Lysis of endothelial cells mediated by complement provides an example of immunologically mediated tissue injury. Presentation of foreign histocompatibility complex antigens by endothelial cells in solid organ allografts can trigger immunologic rejection. In addition, immune-mediated endothelial injury may contribute in some patients with thrombotic thrombocytopenic purpura and in patients with hemolytic uremic syndrome. Thus, in addition to contributing to innate immune responses, endothelial cells participate actively in both humoral and cellular limbs of the immune response.

Endothelial cells can also regulate growth of the subjacent smooth-muscle cells. Heparan sulfate glycosaminoglycans elaborated by endothelial cells can hold smooth-muscle proliferation in check. In contrast, when exposed to various injurious stimuli, endothelial cells can elaborate growth factors and chemoattractants, such as platelet-derived growth factor, that can promote the migration and proliferation of vascular smooth-muscle cells. Dysregulated elaboration of these growth-stimulatory molecules may promote smooth-muscle accumulation in arterial hyperplastic diseases, including atherosclerosis and in-stent stenosis.

Clinical Assessment of Endothelial Function

Endothelial function can be assessed noninvasively and invasively, and typically involves evaluating one measure of endothelial behavior in vivo, viz., endothelium-dependent vasodilation. Using either pharmacologic or mechanical agonists, the endothelium is stimulated to release acutely molecular effectors that alter underlying smooth-muscle cell tone. Invasively, endothelial function can be assessed with the use of agonists that stimulate release of endothelial NO, such as the cholinergic agonists acetylcholine and methacholine. The typical approach involves measuring quantitatively the change in coronary diameter in response to an intracoronary infusion of these short-lived, rapidly acting agents. Noninvasively, endothelial function can be assessed in the forearm circulation by performing occlusion of brachial artery blood flow with a blood pressure cuff, after which the cuff is deflated and the change in brachial artery blood flow and diameter are measured ultrasonographically (Fig. 1-2). This approach depends upon shear stress-dependent changes in endothelial release of NO following restoration of blood flow, as well as the effect of adenosine released (transiently) from ischemic tissue in the forearm.

Typically, the change in vessel diameter detected by these invasive and noninvasive approaches is ~10%. In individuals with frank atherosclerosis or risk factors for atherosclerosis (especially hypertension, hypercholesterolemia, diabetes mellitus, and smoking), such studies can detect endothelial dysfunction as defined by a smaller change in diameter and, in the extreme case, a so-called paradoxical vasoconstrictor response owing to the direct effect of cholinergic agonists on vascular smooth-muscle cell tone.

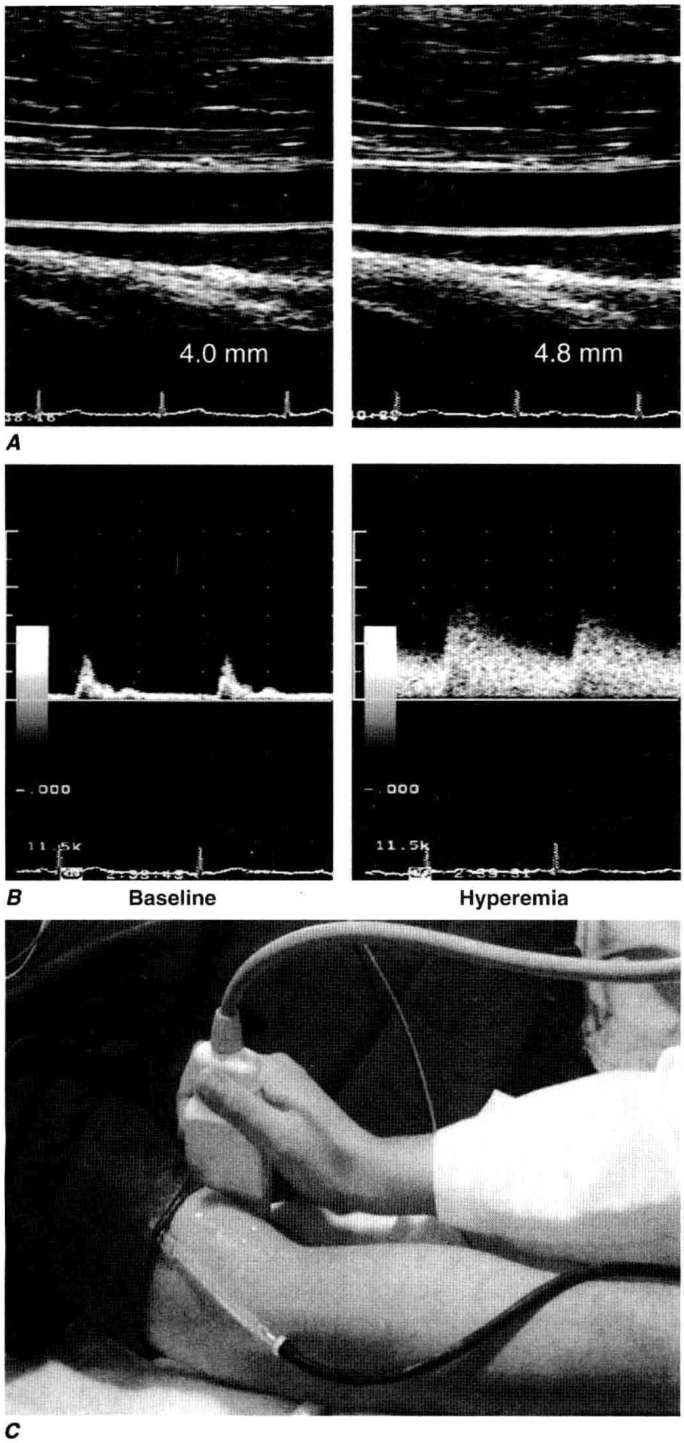


FIGURE 1-2

Assessment of endothelial function in vivo using blood pressure cuff-occlusion and release. Upon deflation of the cuff, changes in diameter (***A***) and blood flow (***B***) of the brachial artery are monitored with an ultrasound probe (***C***). *(Reproduced with permission of J. Vita, MD.)*

VASCULAR SMOOTH-MUSCLE CELL

The vascular smooth-muscle cell, the major cell type of the media layer of blood vessels, also actively contributes to vascular pathobiology. Contraction and relaxation of smooth-muscle cells at the level of the muscular arteries controls blood pressure and, hence, regional blood flow and the afterload experienced by the left ventricle (see later). The vasomotor tone of veins, governed by smooth-muscle cell tone, regulates the capacitance of the venous tree and influences the preload experienced by both ventricles. Smooth-muscle cells in the adult vessel seldom replicate. This homeostatic quiescence of smooth-muscle cells changes under conditions of arterial injury or inflammatory activation. Proliferation and migration of arterial smooth-muscle cells can contribute to the development of arterial stenoses in atherosclerosis, of arteriolar remodeling that can sustain and propagate hypertension, and of the hyperplastic response of arteries injured by angioplasty or stent deployment. In the pulmonary circulation, smooth-muscle migration and proliferation contribute decisively to the pulmonary vascular disease that gradually occurs in response to sustained high-flow states, such as left-to-right shunts. Such pulmonary vascular disease provides a major obstacle to the management of many patients with adult congenital heart disease.

Smooth-muscle cells also secrete the bulk of vascular extracellular matrix. Excessive production of collagen and glycosaminoglycans contributes to the remodeling and altered biology and biomechanics of arteries affected by hypertension or atherosclerosis. In larger elastic arteries, the elastin synthesized by smooth-muscle cells serves to maintain not only normal arterial structure but also hemodynamic function. The ability of the larger arteries, such as the aorta, to store the kinetic energy of systole promotes tissue perfusion during diastole. Arterial stiffness associated with aging or disease, as manifested by a widening pulse pressure, increases left ventricular afterload and portends a poor prognosis.

Like endothelial cells, vascular smooth-muscle cells do not merely respond to vasomotor or inflammatory stimuli elaborated by other cell types but can themselves serve as a source of such stimuli. For example, when stimulated by bacterial endotoxin, smooth-muscle cells can elaborate large quantities of proinflammatory cytokines, such as interleukin 6, as well as lesser quantities of many other proinflammatory mediators. Like endothelial cells, upon inflammatory activation, arterial smooth-muscle cells can produce prothrombotic mediators, such as tissue factor, the antifibrinolytic protein PAI-1, and other molecules that modulate thrombosis and fibrinolysis. Smooth-muscle cells may also elaborate autocrine growth factors that can amplify hyperplastic responses to arterial injury.

Vascular Smooth-Muscle Cell Function

A principal function of vascular smooth-muscle cells is to maintain vessel tone. Vascular smooth-muscle cells contract when stimulated by a rise in intracellular calcium

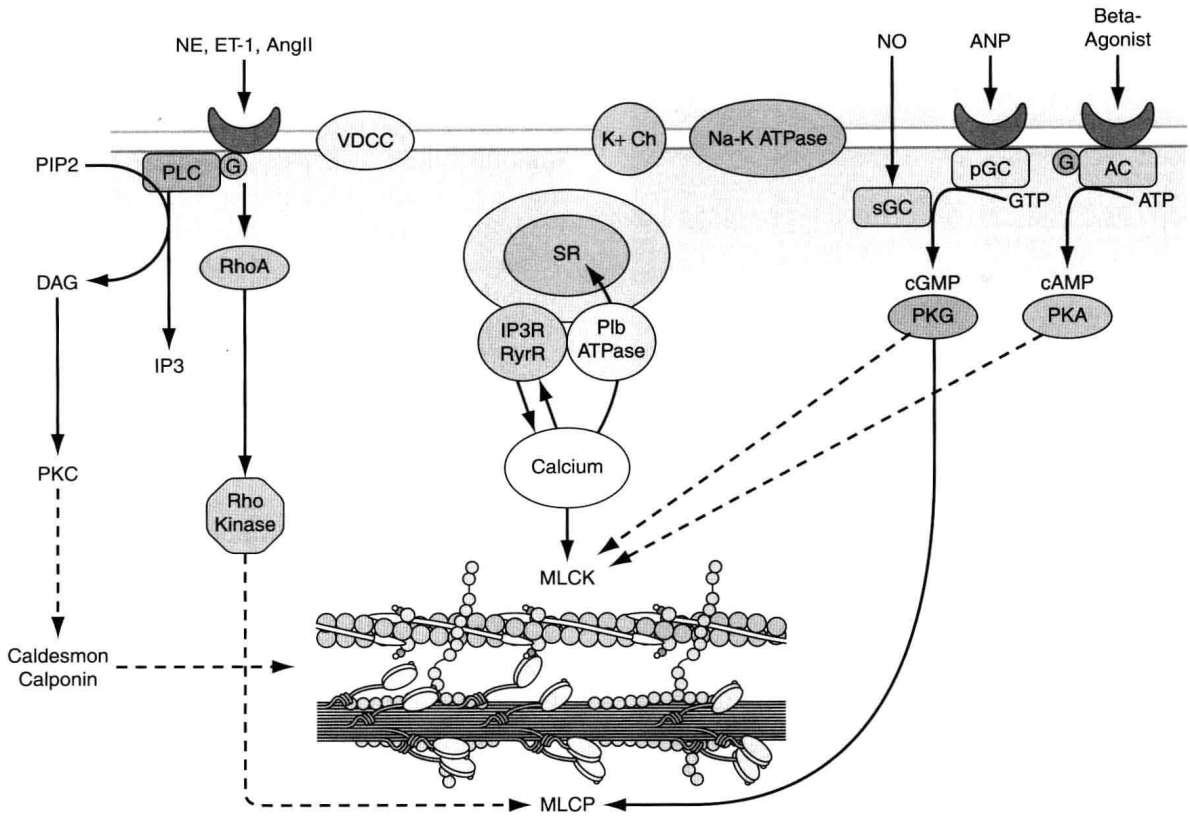


FIGURE 1-3
Regulation of vascular smooth-muscle cell calcium concentration and actomyosin ATPase-dependent contraction. NE, norepinephrine; ET-1, endothelin-1; AngII, angiotensin II; PIP_2, phosphatidylinositol 4,5-biphosphate; PLC, phospholipase C; DAG, diacylglycerol; G, G-protein; VDCC, voltage-dependent calcium channel; IP_3, inositol 1,4,5-trisphosphate; PKC, protein kinase C; SR, sarcoplasmic reticulum; NO, nitric oxide; ANP, antrial natriuretic peptide; pGC, particular guanylyl cyclase; AC, adenylyl cyclase; sGC, soluble guanylyl cyclase; PKG, protein kinase G; PKA, protein kinase A; MLCK, myosin light chain kinase; MLCP, myosin light chain phosphatase. *(Modified from B Berk, in Vascular Medicine, 3d ed, p 23. Philadelphia, Saunders, Elsevier, 2006; with permission.)*

concentration by calcium influx through the plasma membrane and by calcium release from intracellular stores (Fig. 1-3). In vascular smooth-muscle cells, voltage-dependent L-type calcium channels open with membrane depolarization, which is regulated by energy-dependent ion pumps such as the Na^+,K^+-ATPase and ion channels such as the Ca^{2+}-sensitive K^+ channel. Local changes in intracellular calcium concentration, termed *calcium sparks*, result from the influx of calcium through the voltage-dependent calcium channel and are caused by the coordinated activation of a cluster of ryanodine-sensitive calcium release channels in the sarcoplasmic reticulum (see later). Calcium sparks lead to a further direct increase in intracellular calcium concentration and indirectly increases intracellular calcium concentration by activating chloride channels. In addition, calcium sparks reduce contractility by activating large-conductance calcium-sensitive K^+ channels, hyperpolarizing the cell membrane and thereby limiting further voltage-dependent increases in intracellular calcium.

Biochemical agonists also increase intracellular calcium concentration, doing so by receptor-dependent activation of phospholipase C with hydrolysis of phosphatidylinositol 4,5-bisphosphate with generation of diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP_3). These membrane lipid derivatives, in turn, activate protein kinase C and increase intracellular calcium concentration. In addition, IP_3 binds to its specific receptor found in the sarcoplasmic reticulum membrane to increase calcium efflux from this calcium storage pool into the cytoplasm.

Vascular smooth-muscle cell contraction is principally controlled by the phosphorylation of myosin light chain, which, in the steady state, depends on the balance between the actions of myosin light chain kinase and myosin light chain phosphatase. Myosin light chain kinase is activated by calcium through the formation of a calcium-calmodulin complex; with phosphorylation of myosin light chain by this kinase, the myosin ATPase activity is increased and contraction sustained. Myosin light chain phosphatase dephosphorylates myosin light

chain, reducing myosin ATPase activity and contractile force. Phosphorylation of the myosin binding subunit (thr695) of myosin light chain phosphatase by Rho kinase inhibits phosphatase activity and induces calcium sensitization of the contractile apparatus. Rho kinase is itself activated by the small GTPase RhoA, which is stimulated by guanosine exchange factors and inhibited by GTPase-activating proteins.

Both cyclic AMP and cyclic GMP relax vascular smooth-muscle cells, doing so by complex mechanisms. β-Agonists acting through their G-protein-coupled receptors activate adenylyl cyclase to convert ATP to cyclic AMP; NO and atrial natriuretic peptide acting directly and via a G-protein-coupled receptor, respectively, activate guanylyl cyclase to convert GTP to cyclic GMP. These agents, in turn, activate protein kinase A and protein kinase G, respectively, which inactivates myosin light chain kinase and decreases vascular smooth-muscle cell tone. In addition, protein kinase G can directly interact with the myosin-binding substrate subunit of myosin light chain phosphatase, increasing phosphatase activity and decreasing vascular tone. Lastly, several mechanisms drive NO-dependent, protein kinase G–mediated reductions in vascular smooth-muscle cell calcium concentration, including phosphorylation-dependent inactivation of RhoA; decreased IP_3 formation; phosphorylation of the IP_3 receptor–associated cyclic GMP kinase substrate, with subsequent inhibition of IP_3 receptor function; phosphorylation of phospholamban, which increases calcium ATPase activity and sequestration of calcium in the sarcoplasmic reticulum; and protein kinase G–dependent stimulation of plasma membrane calcium ATPase activity, perhaps by activation of the Na^+,K^+-ATPase or hyperpolarization of the cell membrane by activation of calcium-dependent K^+ channels.

Control of Vascular Smooth-Muscle Cell Tone

Vascular smooth-muscle cell tone is governed by the autonomic nervous system and by the endothelium in tightly regulated control networks. Autonomic neurons enter the blood vessel media from the adventitia and modulate vascular smooth-muscle cell tone in response to baroreceptors and chemoreceptors within the aortic arch and carotid bodies, and in response to thermoreceptors in the skin. These regulatory components comprise rapidly acting reflex arcs modulated by central inputs that respond to sensory inputs (olfactory, visual, auditory, and tactile) as well as emotional stimuli. Autonomic regulation of vascular tone is mediated by three classes of nerves: *sympathetic*, whose principal neurotransmitters are epinephrine and norepinephrine; *parasympathetic*, whose principal neurotransmitter is acetylcholine; and *nonadrenergic/noncholinergic*, which include two subgroups—nitrergic, whose principal neurotransmitter is NO; and peptidergic, whose principal neurotransmitters are substance P, vasoactive intestinal peptide, calcitonin gene-related peptide, and ATP.

Each of these neurotransmitters acts through specific receptors on the vascular smooth-muscle cell to modulate intracellular calcium and, consequently, contractile tone. Norepinephrine activates α receptors and epinephrine activates α and β receptors (adrenergic receptors); in most blood vessels, norepinephrine activates postjunctional α_1 receptors in large arteries, and α_2 receptors in small arteries and arterioles, leading to vasoconstriction. Most blood vessels express β_2 adrenergic receptors on their vascular smooth-muscle cells and respond to β agonists by cyclic AMP–dependent relaxation. Acetylcholine released from parasympathetic neurons binds to muscarinic receptors (of which there are five subtypes, M_1–M_5) on vascular smooth-muscle cells to yield vasorelaxation. In addition, NO stimulates presynaptic neurons to release acetylcholine, which can stimulate release of NO from the endothelium. Nitrergic neurons release NO produced by neuronal NO synthase, which causes vascular smooth-muscle cell relaxation via the cyclic GMP–dependent and –independent mechanisms described above. The peptidergic neurotransmitters all potently vasodilate, acting either directly or through endothelium-dependent NO release to decrease vascular smooth-muscle cell tone.

The endothelium modulates vascular smooth-muscle tone by the direct release of several effectors, including NO, prostacyclin, and endothelium-derived hyperpolarizing factor, all of which cause vasorelaxation; and endothelin, which causes vasoconstriction. The release of these endothelial effectors of vascular smooth-muscle cell tone is stimulated by mechanical (shear stress, cyclic strain, etc.) and biochemical mediators (purinergic agonists, muscarinic agonists, peptidergic agonists), with the biochemical mediators acting through endothelial receptors specific to each class.

In addition to these local, paracrine modulators of vascular smooth-muscle cell tone, circulating mediators can also affect tone, including norepinephrine and epinephrine, vasopressin, angiotensin II, bradykinin, and the natriuretic peptides (ANP, BNP, CNP, and DNP), as discussed above.

VASCULAR REGENERATION

Growing new blood vessels can occur in response to conditions such as chronic hypoxia or tissue ischemia. Growth factors, including vascular endothelial growth factor, activate a signaling cascade that stimulates endothelial proliferation and tube formation, defined as *angiogenesis*. The development of collateral vascular networks in the ischemic myocardium reflects this process and can result from selective activation of endothelial progenitor cells, which may reside in the blood vessel wall or home