Contents

Foreword: The Sounds of Progress xvii
Bimal H. Ashar

Preface: Continuing Challenges and Unresolved Problems in Hypertensive Diseases xix
Edward D. Frohlich

Hypertension: New and Future Challenges 1
Edward D. Frohlich

This article provides a preview to the forthcoming articles in this issue, which are written by well-known and authoritative authors for the readers’ pleasure and reference. This article hopes to provide a general overview that stimulates interest, better understanding, and continued joint commitment to the important subject of hypertension.

Diastolic Dysfunction and Hypertension 7
Wilson Nadruz, Amil M. Shah, and Scott D. Solomon

Left ventricular (LV) diastolic dysfunction (LVDD) is characterized by alterations in LV diastolic filling, and is a strong predictor of cardiovascular events and heart failure. Hypertension is the most important risk factor for LVDD in the community and promotes LVDD through several mechanisms, including hemodynamic overload and myocardial ischemia. Associated factors such as age, ethnicity, dietary sodium, obesity, diabetes mellitus, and chronic kidney disease also contribute to LVDD in hypertensive individuals. Blood pressure lowering using antihypertensive medications can improve LVDD; however, it remains unclear whether this improvement in LV diastolic function can improve cardiovascular outcomes.

Heart Failure and Hypertension: Importance of Prevention 19
Marc A. Pfeffer

This article discusses the role of hypertension in heart failure. Elevated blood pressure has the greatest population attributable risk for the development of heart failure. The mortality rates following the clinical recognition of heart failure is increased multifold. The treatment of hypertension with antihypertensive agents is particularly effective in preventing heart failure, which makes it the most effective therapy for heart failure.

Hypertension, Left Ventricular Hypertrophy, and Myocardial Ischemia 29
Tony Stanton and Francis G. Dunn

The risks associated with hypertension emerge through a series of complex interactions. Myocardial ischemia is the major contributor to this
The mechanisms driving ischemia reflect many of the key factors in hypertension, including endothelial and neurohumoral factors, fibrosis, and hemodynamics. Left ventricular hypertrophy and fibrosis are of fundamental importance and together with hemodynamics provide an optimal template for myocardial ischemia. Understanding the pathophysiology has aided a more rational management approach but challenges remain which, if surmounted, will have an impact on the morbidity and mortality caused by myocardial ischemia in patients with hypertension.

The Hypertensive Myocardium: From Microscopic Lesions to Clinical Complications and Outcomes

María U. Moreno, Rocío Eiros, Juan J. Gavira, Catalina Gallego, Arantxa González, Susana Ravassa, Begoña López, Javier Beaumont, Gorka San José, and Javier Díez

The chronic hemodynamic load imposed by hypertension on the left ventricle leads to lesions in the myocardium that result in structural remodeling, which provides support for alterations in cardiac function, perfusion, and electrical activity that adversely influence the clinical evolution of hypertensive heart disease. Management must include detecting, reducing, and reversing left ventricular hypertrophy, as well as the detection and repair of microscopic lesions responsible for myocardial remodeling. Reducing the burden associated with hypertensive heart disease can be targeted using personalized treatment. The noninvasive, biomarker-mediated identification of subsets of patients with hypertensive heart disease is essential to provide personalized treatment.

Hypertension in Patients with Cardiac Transplantation

Amanda L. Bennett and Hector O. Ventura

Hypertension is a common complication among post cardiac transplant recipients affecting more than 95% of patients. Increased blood pressure poses a significant cardiovascular morbidity and mortality in these patients; it should be identified quickly and needs to be managed appropriately. Understanding the pathophysiology and contributing factors to this disease in these complex and unique patients is the key to appropriate treatment selection.

Renal Arterial Disease and Hypertension

Stephen C. Textor

Renal artery disease produces a spectrum of progressive clinical manifestations ranging from minor degrees of hypertension to circulatory congestion and kidney failure. Moderate reductions in renal blood flow do not induce tissue hypoxia or damage, making medical therapy for renovascular hypertension feasible. Several prospective trials indicate that optimized medical therapy using agents that block the renin-angiotensin system should be the initial management. Evidence of progressive disease and/or treatment failure should allow recognition of high-risk subsets that benefit from renal revascularization. Severe reductions in kidney blood flow ultimately activate inflammatory pathways that do not reverse with restoring blood flow alone.
Significant hemodynamic changes ensue with aging, leading to an ever-growing epidemic of hypertension. Alterations in central arterial properties play a major role in these hemodynamic changes. These alterations are characterized by an initial decline in aortic distensibility and an increase of diastolic blood pressure, followed by a sharp increase in pulse wave velocity (PWV), and an increase in pulse pressure (PP) beyond the sixth decade. However, the trajectories of PWV and PP diverge with advancing age. There is an increased prevalence of salt-sensitive hypertension with advancing age that is, in part, mediated by marinobufagenin, an endogenous sodium pump ligand.

Heart failure and chronic renal diseases are usually progressive and only partially amenable to therapy. These disorders can be the sequelae of hypertension or worsened by hypertension. They are associated with the tissue up-regulation of multiple peptides, many of which are capable of acting within the cell interior. This article proposes that these peptides, intracrines, can form self-sustaining regulatory loops that can spread through heart or kidney, producing progressive disease. Moreover, mineralocorticoid activation seems capable of amplifying some of these peptide networks. This view suggests an expanded explanation of the pathogenesis of progressive cardiorenal disease and suggests new approaches to treatment.

The presence of local renin angiotensin aldosterone systems (RAAS) in the cardiovascular and renal tissues and their influence in cardiovascular and renal diseases are described. The fundamental role of ACE/Ang II/AT1 receptor axis activation as well the counterregulatory role of ACE2/Ang (1–7)/Mas receptor activation on cardiovascular and renal physiology and pathology are emphasized. The presence of a local RAS and its influence on hypertension is discussed, and finally, the hypothesis that epigenetic factors change the RAAS in utero and induce the expression of renin or Ang II inside the cells of the cardiovascular system is presented.

In the United States, more than 50 million people have blood pressure at or above 120/80 mm Hg. All components of cardiorenal metabolic syndrome (CRS) are linked to metabolic abnormalities and obesity. A major driver for CRS is obesity. Current estimates show that many of those with hypertension and CRS show some degree of systemic and cardiovascular insulin...
Resistance. Several pathophysiologic factors participate in the link between hypertension and CRS. This article updates recent literature with a focus on the function of insulin resistance, obesity, and renin angiotensin aldosterone system-mediated oxidative stress on endothelial dysfunction and the pathogenesis of hypertension.

**Obesity: A Perspective from Hypertension**
Dinko Susic and Jasmina Varagic

The prevalence of obesity-related hypertension is high worldwide and has become a major health issue. The mechanisms by which obesity relates to hypertensive disease are still under intense research scrutiny, and include altered hemodynamics, impaired sodium homeostasis, renal dysfunction, autonomic nervous system imbalance, endocrine alterations, oxidative stress and inflammation, and vascular injury. Most of these contributing factors interact with each other at multiple levels. Thus, as a multifactorial and complex disease, obesity-related hypertension should be recognized as a distinctive form of hypertension, and specific considerations should apply in planning therapeutic approaches to treat obese individuals with high blood pressure.

**Patient Management of Hypertensive Subjects without and with Diabetes Mellitus Type II**
Michel E. Safar, Jacques Blacher, and Athanase D. Protogerou

The description of blood pressure (BP) curve has evolved to include several noninvasively determined parameters, such as aortic stiffness, BP variability, wave reflections, and pulse pressure amplification. These techniques are likely to improve the efficacy of assessing pulsatile arterial hemodynamics and changes in arterial stiffness. The goal for future antihypertensive treatments should not only reduce steady BP, but also control pulsatile pressure and modify the stiffness gradient between central and peripheral arteries, which is frequently elevated. These changes have the potential to reduce residual cardiovascular risk but also to define drug strategies adapted to the needs of individual hypertensive subjects.

**Oxidative Stress and Hypertensive Diseases**
Roxana Loperena and David G. Harrison

It has become clear that reactive oxygen species (ROS) contribute to the development of hypertension via myriad effects. ROS are essential for normal cell function; however, they mediate pathologic changes in the brain, the kidney, and blood vessels that contribute to the genesis of chronic hypertension. There is also emerging evidence that ROS contribute to immune activation in hypertension. This article discusses these events and how they coordinate to contribute to hypertension and its consequent end-organ damage.

**What Have We Learned from the Genetics of Hypertension?**
Friedrich C. Luft

Twin studies show that about half the risk of hypertension development is inherited. Mendelian hypertension has elucidated astounding basic
pathways contributing to hypertension over (presumably) dietary salt intake or directly through increased peripheral vascular resistance. The Mendelian mutations exercise large effects on blood pressure. Inversely, studying the entire human genome for sources signaling blood pressure has yielded many signals with small effects. Thus far, few loci have been validated or translated into targets. Both genetic strategies are necessary, and much remains to be done.

The Kidney in Hypertension 207
Hillel Sternlicht and George L. Bakris

Hypertension is the second most common cause of chronic kidney disease (CKD) and is a potentiator of kidney failure when accompanying disease. CKD is a common cause of resistant hypertension. Nephropathy progression has dramatically slowed over the past 3 decades from an average of 8 to between 2–3 mL/min per year regardless of diabetes status. The incidence of very high albuminuria as well as progression from high albuminuria very high albuminuria has substantially decreased over the past 3 decades. This improvement relates to better blood pressure control using agents that slow nephropathy as well as better glycemic and cholesterol control.

Guidelines for the Management of Hypertension 219
Aram V. Chobanian

This article summarizes pertinent data from clinical trials on the effects of antihypertensive therapy on cardiovascular complications. Prior definitions of hypertension and blood pressure goals of therapy are discussed, and differences between national and international guidelines on such goals are summarized. The results of the SPRINT study are summarized, and the impact of this study on future goals of treatment is discussed. New recommendations are provided on blood pressure goals, and the effects such goals might have on clinical practice are discussed.

Adherence to Antihypertensive Therapy 229
Erin Peacock and Marie Krousel-Wood

Adherence to antihypertensive medication remains a key modifiable factor in the management of hypertension. The multidimensional nature of adherence and blood pressure (BP) control call for multicomponent, patient-centered interventions to improve adherence. Promising strategies to improve antihypertensive medication adherence and BP control include regimen simplification, reduction of out-of-pocket costs, use of allied health professionals for intervention delivery, and self-monitoring of BP. Research to understand the effects of technology-mediated interventions, mechanisms underlying adherence behavior, and sex-race differences in determinants of low adherence and intervention effectiveness may enhance patient-specific approaches to improve adherence and disease control.