Over the past four or five decades, hypertension and cardiovascular medicine has experienced dramatic and innovative changes that have significantly reduced morbidity and mortality. A vast array of new antihypertensive compounds have been developed, which are able to inhibit many pathophysiologic mechanisms of the disease and prevent many of the outcomes in patients with hypertension. Much of this series of therapeutic breakthroughs have been the result of active participation of clinical scientists with tremendous and remarkable knowledge of and experience with the fundamental mechanisms of disease. In more recent years, much new information has appeared concerning the basis genetic and biologic mechanisms involved in cardiovascular and renal diseases. What remains of utmost importance is for members of the academic community with a wide spectrum of experience and points of view to continue to work with the fundamental problems and mechanisms of the diseases.
Hypertension (HTN) is a leading risk factor for cardiovascular disease (CVD) and chronic kidney disease (CKD)-related morbidity and mortality. Several abnormalities participate in the development of HTN. Inappropriately activated systemic and local tissue renin angiotensin aldosterone systems (RAAS) contribute to the hemodynamic and metabolic abnormalities that lead to endothelial dysfunction, HTN, CVD, and CKD. There is a growing body of evidence demonstrating a close relationship between RAAS activation, excessive production of reactive oxygen species, insulin resistance, and HTN. From a therapeutic standpoint, RAAS blockade results in improved insulin resistance, glucose homeostasis, and improved cardiovascular and renal outcomes. This article is focused on the role of RAAS-mediated insulin resistance and oxidative stress in the pathogenesis of HTN, CVD, and CKD.

Arterial Aging and Subclinical Arterial Disease are Fundamentally Intertwined at Macroscopic and Molecular Levels

Edward G. Lakatta, Mingyi Wang, and Samer S. Najjar

The structure and function of arteries change throughout a lifetime. Age is the dominant risk factor for hypertension, coronary heart disease, congestive heart failure, and stroke. The cellular/molecular proinflammatory alterations that underlie arterial aging are novel putative candidates to be targeted by interventions aimed at attenuating arterial aging as a major risk factor for cardiovascular diseases. This review provides a landscape of central arterial aging and age-disease interactions, integrating perspectives that range from humans to molecules, with the goal that future therapies for cardiovascular diseases, such as hypertension, also will target the prevention or amelioration of unsuccessful arterial aging.

Hypertension, Systolic Blood Pressure, and Large Arteries

Michel E. Safar

This article discusses the following: (1) factors modulating central and peripheral SBP and PP in hypertensive subjects; (2) mechanisms enhancing PP variations in this population; (3) Analysis of pulsatile arterial hemodynamics as predictors of CV risk; and (4) Pulsatile hemodynamics and strategies lowering CV risk in the treatment of hypertension.

Oxidative Stress and Hypertension

David G. Harrison and Maria Carolina Gongora

 Reactive oxygen species (ROS) oxidize, reduce, or combine with other molecules in both physiologic and pathophysiologic ways. This article examines the role of ROS in hypertension, especially in certain tissues, such as the brain, the kidney, and the vasculature. A major clinical challenge is that the routinely used antioxidants are ineffective in preventing or treating...
cardiovascular disease and hypertension. This is likely because these
drugs are either ineffective or act in a nontargeted fashion, such that
they remove not only injurious ROS but also those involved in normal
cell signaling. Inflammatory cells such as T cells may contribute to hyper-
tension, and further investigation of how this occurs may lead to new
therapies.

Towards a New Paradigm About Hypertensive Heart Disease 637
Javier Díez

A new paradigm is emerging related to the impact of chronic hypertension
on the cardiac parenchyma. Whereas left ventricular hypertrophy may be
detected early and accurately in hypertensive patients by electrocardiog-
raphy and echocardiography, newer cardiac imaging methods and the
monitoring of several circulating biomarkers holds promise as a noninva-
sive tool for the diagnosis of myocardial remodeling. A large number of
clinical studies have shown that long-term antihypertensive treatment
may be associated with regression of left ventricular hypertrophy, and
this is associated with the decrease of the risk of cardiovascular morbidity
and mortality. However, because the remaining risk is unacceptably high,
new therapeutic strategies aimed not just to decrease left ventricular
mass, but also to repair myocardial remodeling are necessary. All of these
aspects are reviewed in brief in this article.

Diastolic Dysfunction as a Link Between Hypertension and Heart Failure 647
Anil Verma and Scott D. Solomon

Hypertension significantly contributes to cardiovascular morbidity and
mortality by causing substantial structural and functional adaptations,
including left ventricular diastolic dysfunction. Left ventricular diastolic
dysfunction is characterized by abnormalities in left ventricular filling,
including decreased diastolic distensibility and impaired relaxation, and
it may represent an early measure of myocardial end-organ damage. Dia-
stolic dysfunction may well precede development of left ventricular hyper-
trophy in hypertension and possibly is characteristic of an important
pathophysiologic link between hypertension and heart failure with pre-
served ejection fraction. No specific therapeutic regimen has shown to
benefit patients who have heart failure with preserved ejection fraction,
and thus there is a need to understand the potential mechanisms primarily
responsible for this clinical syndrome and its relationship to hypertension
and diastolic dysfunction.

Hypertension and Cardiac Failure in its Various Forms 665
Krishna K. Gaddam, Anil Verma, Mark Thompson, Rohit Amin,
and Hector Ventura

Aging population and poorly controlled hypertension contribute to an ever-
increasing prevalence of heart failure. Two different phenotypes of heart
failure, namely, heart failure with reduced ejection fraction and heart failure
with preserved ejection fraction, are being increasingly recognized. However, they may not necessarily be separate processes and may actually represent a continuum. Nevertheless, either form of heart failure is associated with very high morbidity and mortality. Significant advances have been achieved in understanding the pathophysiology and treatment of patients who have heart failure with reduced ejection fraction. However, heart failure with preserved ejection fraction is less well understood and no convincing evidence-based treatment options are available in treating these patients. Given the poor prognosis with either form of heart failure, it is imperative to recognize and treat hypertension early.

Hypertension and Myocardial Ischemia 681
Brian P. Murphy, Tony Stanton, and Francis G. Dunn

There is an impressive evidence base for the presence of myocardial ischemia in patients who have hypertension. This relationship ranges from the obvious association with obstructive coronary artery disease to more subtle mechanisms related to hemodynamic, microcirculatory, and neuroendocrine abnormalities. All of these factors serve to destabilize the critical balance between myocardial oxygen supply and demand. We have at our disposal a range of sophisticated investigations that allow us to demonstrate the presence and extent of the ischemia and therefore to target specific therapies to reduce the risk to these patients. Achieving target blood pressure and managing all reversible components of the patient’s cardiovascular risk status help to minimize the clinical sequelae of myocardial ischemia in this vulnerable population.

The Kidney, Hypertension, and Remaining Challenges 697
Nitin Khosla, Rigas Kalaitzidis, and George L. Bakris

There is an epidemic of chronic kidney disease in the Western world, with hypertension being the second most common cause. Blood pressure control rates, while improving, are still below 50% for the United States population. The following three challenges remain for the treatment of hypertension and associated prevention of end-stage kidney disease. First, a better understanding by the general medical community of how and in whom to use renin angiotensin aldosterone system blockers is needed. Second, the appropriate initiation of fixed-dose combination therapy to achieve blood-pressure goals needs to be clarified. Finally, the subgroup of patients with kidney disease needs more aggressive blood pressure lowering.

Current Approaches to Renovascular Hypertension 717
Stephen C. Textor

This article examines the status regarding prevalence, mechanisms, clinical manifestations and management of renovascular hypertension at this point in time. It should be viewed as a work in progress. As with most complex conditions, clinicians must integrate the results of published literature studies while considering each patient’s specific features and comorbid
Beyond identifying renovascular disease as a cause of secondary hypertension, one must manage renal artery stenosis (RAS) itself as an atherosclerotic vascular complication. This disease warrants follow-up regarding progression and potential for ischemic tissue injury. These elements often determine the role and timing for revascularization. In this respect, atherosclerotic renal artery stenosis is analogous to progressive carotid or aortic aneurysmal disease.

Obesity and Hypertension: Mechanisms, Cardio-Renal Consequences, and Therapeutic Approaches 733

Efrain Reisin and Avanelle V. Jack

Obesity and its relationship to hypertension is growing worldwide and is considered today to be a pandemic. This article focuses on the impact of obesity and hypertension on the cardiovascular and renal systems. It also summarizes the nonpharmacological and pharmacological approaches used to control hypertension in the obese population.

Barriers to and Determinants of Medication Adherence in Hypertension Management: Perspective of the Cohort Study of Medication Adherence Among Older Adults 753

Marie A. Krousel-Wood, Paul Muntner, Tareq Islam, Donald E. Morisky, and Larry S. Webber

Low adherence to antihypertensive medication remains a public health challenge. Understanding barriers to, and determinants of, adherence to antihypertensive medication may help identify interventions to increase adherence and improve outcomes. The Cohort Study of Medication Adherence in Older Adults is designed to assess risk factors for low antihypertensive medication adherence, explore differences across age, gender, and race subgroups, and determine the relationship of adherence with blood pressure control and cardiovascular outcomes over time. This article discusses the relevance of this study in addressing the issue of barriers to antihypertensive medication adherence.