

Updates in Hypertension and Cardiovascular Protection
Series Editors: Giuseppe Mancia · Enrico Agabiti Rosei

Adel E. Berbari
Giuseppe Mancia *Editors*

Disorders of Blood Pressure Regulation

Phenotypes, Mechanisms, Therapeutic
Options



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Updates in Hypertension and Cardiovascular Protection

Series Editors

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The aim of this series is to provide informative updates on both the knowledge and the clinical management of a disease that, if uncontrolled, can very seriously damage the human body and is still among the leading causes of death worldwide. Although hypertension is associated mainly with cardiovascular, endocrine, and renal disorders, it is highly relevant to a wide range of medical specialties and fields – from family medicine to physiology, genetics, and pharmacology. The topics addressed by volumes in the series *Updates in Hypertension and Cardiovascular Protection* have been selected for their broad significance and will be of interest to all who are involved with this disease, whether residents, fellows, practitioners, or researchers.

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Editors

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Phenotypes, Mechanisms,
Therapeutic Options



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Preface

Over the last decades progress in our understanding of the pathophysiology, epidemiology, and therapeutic approaches to hypertension has led this condition to be viewed differently from the past. Hypertension, initially classified as primary and secondary, is now subdivided into a much larger number of phenotypes based on demographics, comorbidities, presence or absence of other risk factors, or target organ involvement. Genetic involvement is also now clearer. The aim of this book is to discuss the multiple new aspects (some of which novel) of the hypertension disease. Sections are devoted to the general aspects of hypertension including the clinical importance of blood pressure values different from the conventional office ones, the relevance to pathophysiology and prognosis of circadian rhythm and seasonal variations in blood pressure, the temporal evolution of treated and untreated hypertension, and the factors involved in the appearance and progression of a blood pressure elevation, including the possible contribution of single or, for essential hypertension, multiple genes. Other sections deal with the clinical aspects of hypertension, and the specific therapeutic options for each hypertension phenotype. This extends to prehypertension as well as to white coat, masked, renovascular, endocrine, pediatric, and gestational hypertension. Finally, the book reviews hypertension phenotypes that are less well known and dealt with by classical textbooks, i.e., calculus renal disease, stress-induced hypertension, pseudo-hypertension, paroxysmal pseudo-pheochromocytoma, and other rare causes of blood pressure elevation such as Turner syndrome, hypertension due to herbal and medicinal compounds and drugs, to call attention to these rarer conditions which are nevertheless mechanistically and clinically relevant.

We hope that physicians and investigators interested in hypertension will find the content of the book stimulating and useful to their professional activity.

Beirut, Lebanon
Monza, Italy

Adel E. Berbari
Giuseppe Mancina

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Part I

General Aspects

Introduction: Definition and Classification of Arterial Pressure Phenotypes

1

Lawrence R. Krakoff

1.1 Introduction

The title of this book and the range of topics that are covered in its chapters indicate a large, complex, and ever-growing body of medical science related to blood pressure and, in particular, the application of that science to care of a very large fraction of the globe's human population [1]. The cardiovascular scientist defines blood pressure as the measured force upon the blood at some point from within the heart to the vascular tree from arteries to capillaries to veins and back to the pump. Clinicians usually refer to the measurement of pressure in the upper arm (brachial artery pressure). Much of the population may consider blood pressure to overlap with "pressure," meaning mental stress related to the "pressure" of work, family concerns, and various threats. "Blood pressure" alone may not be the optimal term for all these perspectives, so that more precise and meaningful terms are truly needed for an accurate set of definitions that capture current research in this very important area of cardiovascular medicine.

"Hypertension" or "high blood pressure" has been recognized since the nineteenth century as a disorder in which the systemic arterial pressure is persistently increased above a normal or safe level. The effect of hypertension is its association with adverse consequences for those with the disorder [2]. Initially recognized as a manifestation of chronic kidney disease, hypertension was subsequently identified in many without kidney disease, but who had specific causes for their high blood pressure. However, as the epidemiology of high blood pressure progressed, it soon became apparent that the large majority of those with high blood pressure had no other obvious disorder to account for their condition. Thus, the terms "essential hypertension, primary hypertension, and even idiopathic hypertension" entered

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medical language, and secondary hypertension became the label for the far less common diseases, mostly of the kidneys or adrenal glands. Until the 1960s, clinical classification of normal and high blood pressure was binary and depended, with rare exception, on the stethoscope and mercury manometer of the doctor's office or hospital location.

The past 50 years have seen unprecedented growth in technology, physiology, pathology, pharmacology, epidemiology, and clinical care for those with disorders of systemic arterial pressure. It is now certain that the level of arterial pressure and its variability are traits that define phenotypes and that both genetic patterns and various lifestyles and exposures participate in defining that phenotype. The range of classifications and definitions for characterizing systemic arterial pressure and, most importantly, the linkages between these definitions to cardiovascular risk and its management have rapidly expanded. The following section of this introduction will survey the current classifications relevant to the phenotypes that define high and low arterial pressure that will be the detailed subjects of the following chapters of this book.

1.2 Which Pressure?

Recording the pressure wave form within arteries discloses several specific characteristics: the peak or *systolic pressure* generated by cardiac stroke volume, the lowest pressure between peaks or *diastolic pressure*, and the difference between systolic and diastolic pressure or *pulse pressure*. The mean arterial pressure is the average pressure for the entire cycle and is near to the diastolic pressure plus one third of the pulse pressure.

Brachial artery pressures have been the basis for past assessment of arterial pressure whether in diagnostic studies or randomized trials of antihypertensive therapy. However, the actual systolic and diastolic pressures "seen" or exposed to the coronary, carotid, cerebral, and renal arteries differ from brachial pressures and may be more closely related to pressure-related pathology. Noninvasive methods for assessing *central aortic pressure* have been developed and explored to define large artery properties more precisely than relying on brachial measurements. Measuring central aortic pressure may be a useful supplement for patient management [3]. Likewise assessing stiffness of large arteries has previously depended on the simple difference between systolic and diastolic brachial pressures, i.e., *pulse pressure*, but more accurate techniques relying on aortic pulse wave velocity and analysis of reflected waves are now available and being implemented in clinical research [4].

1.3 Classification of Systemic Arterial Pressure

Table 1.1 displays the definitions for normal and high blood pressure in adults, based on recent guidelines for clinic pressures. The terms isolated systolic hypertension or isolated diastolic hypertension apply when one of the pressures is elevated

Table 1.1 Classification based on level of clinic pressures

Definition	Blood pressure range (mmHg)	Comment/source
Normal-optimal pressure	<120/80	All guidelines
Prehypertension	120–139/80–89	JNC-7 [20]
High normal pressure	130–139/85–89	EHS [21]
Hypertension	≥140/90	Most guidelines
Resistant hypertension	≥140/90	On treatment with 3+ antihypertensive drugs, usually including a diuretic [22]

Table 1.2 Other definitions. Comparison between systolic and diastolic hypertension

Definition	Clinic systolic pressure	Clinic diastolic pressure	Comment
Isolated systolic hypertension	≥140 mmHg	<90 mmHg	In younger (<50) patients associated with high cardiac output. Well-trained athletes Most frequent in patients >50 years related to increased arterial stiffness
Isolated diastolic hypertension	<140 mmHg	≥90 mmHg	Seen in younger patients and associated with increased risk
Exercise hypertension [23]	≥210 mmHg for men ≥190 mmHg for women	≥90 mmHg or ≥10 mmHg increase	Associated with increased risk factors or left ventricular hypertrophy

and the other is not, as shown in Table 1.2. During exercise, systolic pressure increases, but the change in diastolic pressure is less consistent. Also shown in Table 1.2 are criteria for exercise-related hypertension.

In routine clinical care, one or a few pressures are measured with uncertain methods despite available guidelines [5]. Improvement in accuracy for office measurement has been recommended, in part by taking more measurements using automated devices, such as the BpTRU [6].

The determinants of arterial pressure are related to age. Elevated systolic pressure, per se, has a somewhat different pathophysiology and significance for age <50 and older populations. For the elderly, arterial fibrosis and calcification contribute to systolic elevations with wide pulse pressures [7]. Age norms for systolic and diastolic pressures for *pediatric* and *adolescent* populations have been derived that define normal pressure, prehypertension, and hypertension in these age groups. These are based on specific age-related cutoffs for upper 90% and 95% percentiles [8]. This age-related definition of hypertension for children from age 10 and upward is significantly correlated with hypertension in adult life based on a long-term tracking study [9].

For accurate diagnosis or classification, useful and reliable methods are crucial. The development of accurate devices for use in both the clinic and out-of-the-office settings has radically changed the spectrum for classification of systemic blood pressure [10]. In developed nations, ambulatory blood pressure monitors, home