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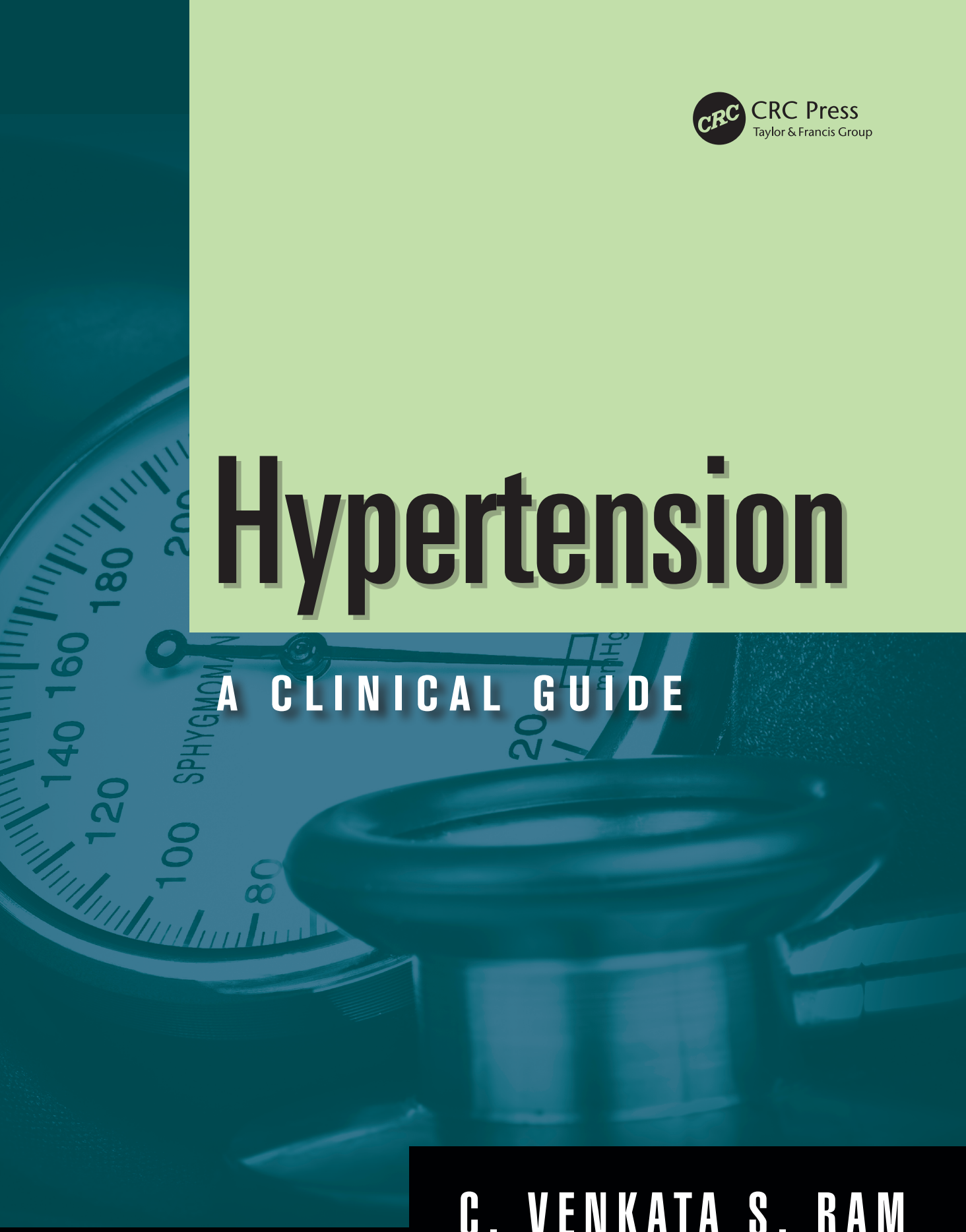
Hypertension

A CLINICAL GUIDE



C. VENKATA S. RAM

HYPERTENSION: A CLINICAL GUIDE

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CRC Press
Taylor & Francis Group
Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Version Date: 20131118

International Standard Book Number-13: 978-1-4822-4045-0 (eBook - PDF)

Contents

Dedication

To my wife Asha for her inspiration, daughters Radha, Gita, and son-in-law Srinivasa Prasad for their love and support.

Preface

Hypertension remains an important risk factor for premature cardiovascular disease and accelerated atherosclerosis. It has become a major public health hazard not only in the so-called industrialized nations, but also in the emerging economies. Hypertension research is increasing rapidly and shedding more light on previously unknown diagnostic and therapeutic aspects of this most prevalent cardiovascular disease risk factor; consequently, the amount of literature published is also growing at an unprecedented pace.

This handbook provides readers with an opportunity to acquire additional knowledge on all the fundamental and practical aspects of hypertension – epidemiology, risk, diagnosis, treatment, and secondary causes. It is designed in an easy-to-read style for busy clinicians and academicians dealing with systemic hypertension and its toxicity. I hope that the readers of this book will be persuaded to acknowledge that hypertension, despite its complexity, can be diagnosed and treated effectively in clinical practice.

The promise of achieving therapeutic targets for global blood pressure control can be fulfilled sooner than we expect, provided early detection combined with effective treatment creates a positive attitude amongst patients and their families. The trust in doctors, with support from the families, can pave the way for adherence to proper treatment which, of course, ultimately depends on an effective healthcare system designed to reduce the disease burden on the community from hypertension.

I am grateful to CRC Press for producing such a high-quality book on a public health problem of global importance and urgency

Dr C. Venkata S. Ram

Acknowledgements

My sincere thanks go to Ms Jill Northcott of CRC Press for her faith in me, her diligent attention to the matter, for giving me invaluable advice, and for our record number of phone conversations regarding the literature on hypertension. I must also thank Kate Nardoni and Peter Beynon for their tremendous assistance and guidance, and for their thorough work in the process of assembling and designing this book.

I also thank Dr Chase Archer for his initial round of editorial assistance and Dr Edgar Lerma for proofing some sections of the book. I am most grateful to Dr Vincent Friedwald for looking at the proofs and revisions with immense care and suggesting some important amendments to the final version. My sincere thanks to Ms Nanci Hassell (Dallas, USA) and Ms Madhawii (Hyderabad, India) for their superb secretarial skills in compiling this book.

Abbreviations

ABPM	ambulatory blood pressure monitoring
ACCOMPLISH	Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (Trial)
ACCORD–BP	Action to Control Cardiovascular Risk in Diabetes – Blood Pressure (Trial)
ACE	angiotensin-converting enzyme
ACTH	adrenocorticotropic hormone
AKI	acute kidney injury
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
ALTITUDE	Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints
ANP	atrial natriuretic peptide
APA	aldosterone-producing adenoma
ARAS	artherosclerotic renal artery stenosis
ARB	angiotensin receptor blocker
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial
AT	angiotensin
BP	blood pressure
CCB	calcium channel blocker
CHF	congestive heart failure
CKD	chronic kidney disease
CO	cardiac output
CTA	computed tomography angiography
CVD	cardiovascular disease
DA_1	dopamine-receptor
DASH	Dietary Approach to Stop Hypertension
DHP	dihydropyridine
DN	diabetic nephrology
DRI	direct renin inhibitor
EDV	end diastolic volume
ESRD	end-stage renal disease
ESV	end systolic volume
ET-1	endothelin-1
FHS	Framingham Heart Study
GFR	glomerular filtration rate
GMP	guanosine monophosphate
HBPM	home blood pressure monitoring
HCTZ	hydrochlorothiazide
IAH	idiopathic adrenal hyperplasia
INVEST	International Verapamil SR-Trandolapril (Study)
JNC 7	Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

LVH	left ventricular hypertrophy
MEN	multiple endocrine neoplasia
MI	myocardial infarction
MIBG	^{123}I-metaiodobenzylguanidine
MRA	magnetic resonance angiography
MRFIT	Multiple Risk Factors Intervention Trial
NE	norepinephrine
NHANES	National Health and Nutrition Examination Survey
NICE	National Institute for Health and Care Excellence
NKF-K/DOQI	National Kidney Foundation – Kidney Disease: Outcome Quality Initiative
NSAID	non-steroidal anti-inflammatory drug
ONTARGET	Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial
PA	primary aldosteronism
PAC	plasma aldosterone concentration
PE	pre-eclampsia
PRA	plasma renin activity
PRoFESS	Prevention Regimen for Effectively Avoiding Second Strokes
RAAS	renin–angiotensin–aldosterone system
RDN	renal denervation
RVHT	renovascular hypertension
SHEP	Systolic Hypertension in the Elderly Program
SNS	sympathetic nervous system
SVR	systemic vascular resistance
TOD	target organ damage
TRANSCEND	Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease
USD	United States dollars
VALUE	Valsartan Antihypertensive Long-Term Use Evaluation (Study)

CHAPTER 1

INTRODUCTION TO HYPERTENSION

Overview

Since the publication of William Harvey's treatise in 1628, it has been recognized that the heart and blood vessels play a critical role in maintaining bodily functions through the provision of circulation to vital organs. The cardiovascular system sustains the metabolic demands of all organs, with the pumping action of the heart being responsible for generating and maintaining an adequate blood supply to all the tissues. This pumping activity of the heart determines cardiac output (CO) which, coupled with systemic vascular resistance (SVR), determines the blood pressure (BP) and blood flow. CO or SVR, or both, can be affected by a number of factors, resulting in an alteration in the normal regulation of BP. *Hypertension* refers to an increase in intra-arterial pressure. Currently, most guidelines around the world define hypertension as systolic BP levels in excess of 140 mmHg or diastolic BP levels greater than 90 mmHg; normal BP is 120/80 mmHg or lower. Any BP level between those two ranges is now called either *prehypertension* or *borderline hypertension*. Large numbers of people both in developed and developing societies throughout the world will eventually develop hypertension at some point in their lifetime (Figure 1.1).

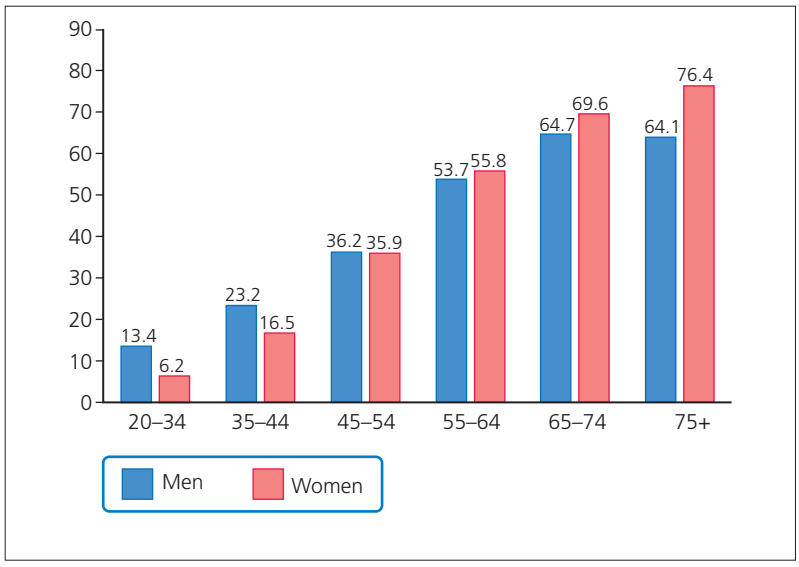


Fig. 1.1 Prevalence of hypertension as a percentage of the population from the National Health and Nutrition Examination Survey observations. (Adapted from Wright JD, Hughes JP, Ostchega Y *et al*. (2011) Mean systolic and diastolic blood pressure in adults aged 18 and over in the United States, 2001–2008. *Natl Health Stat Report* **25(35):**1–22, 24.)

There are many factors that influence the balance between CO and SVR. CO is dependent on both the function (pumping action) of the heart and the circulating volume of blood. In turn, blood volume is strongly influenced by sodium regulation and the fluid handling abilities of the kidneys. Thus, the kidneys play a major role in maintaining fluid and sodium homeostasis, with impairment of kidney function (even of modest degree) causing significant aberrations their ability to regulate fluid volume. SVR is dependent on several characteristics of the blood vessels, including wall thickness and vasomotor tone. In addition, metabolic factors, local environment, and humeral milieu can all affect and influence SVR.

In about 5–10% of cases, hypertension is secondary to a specific cause. In such cases of secondary hypertension, correction of the underlying abnormality will often ameliorate or even completely correct hypertension. In the remaining 90% of patients with *essential* or *primary* hypertension, there may be no obvious cause. Many factors are known to contribute to hypertension including certain lifestyle changes, age, environmental factors, and genetic predisposition. In most cases, even with the varied or unknown etiology of disease, hypertension can be treated or greatly improved with combinations of medication and non-pharmacological treatments. Effective treatment of hypertension is important because successful therapy reduces the risk of morbidity and mortality associated with hypertension.

The initial stages of hypertension are usually asymptomatic, therefore without routine BP monitoring hypertension can go undetected for many years. This makes hypertension truly a 'silent killer'.

Some of the complications associated with hypertension, many of which affect the cardiovascular system at a very early stage, are listed in *Table 1.1*. For example, hypertension can cause cardiac myocardial hypertrophy and vascular remodeling. If left untreated, patients with hypertension are at an increased risk of death from cardiovascular disease (CVD), including stroke, myocardial infarction, heart failure, and other complications. Treatment of hypertension can stop progression of disease and may even reverse target organ damage (TOD). This prospect highlights the need for aggressive treatment of hypertension to reduce and maintain BP at normal levels.

Table 1.1. Some health complications associated with hypertension.

Cardiovascular disease	Other
Congestive heart failure	Chronic kidney disease
Stroke	Hypertensive nephrosclerosis
Myocardial infarction	End-stage renal disease
Left ventricular hypertrophy	Retinopathy
Peripheral arterial disease	

Hypertension and cardiovascular disease

CVD is rapidly emerging as a major global health hazard. In the USA it is now the leading cause of death, with almost one million deaths attributed to CVD annually. CVD includes coronary heart disease, stroke, heart failure, and other related conditions and mainly affects persons over 60 years of age. Hypertension is the major risk factor associated with the development of premature CVD, ahead of cigarette smoking, diabetes, and dyslipidemia. The effect of BP on cardiovascular risk is progressive and continuous as the pressure increases, such that patients with high BP levels are at greater risk of developing congestive heart failure (CHF) than those with low BP levels (Figures 1.2 and 1.3). The risk is conferred on all age groups and with any combination of additional risk factors, which can exacerbate morbidity and mortality. However, even with all of the evidence that hypertension is a contributing factor to CVD, mortality directly caused by hypertension can be difficult to determine. The use of death certificates to determine total numbers of deaths associated with a particular condition is based on a record of the immediate cause of death (e.g. heart failure or stroke), which underestimates the underlying influence of hypertension.

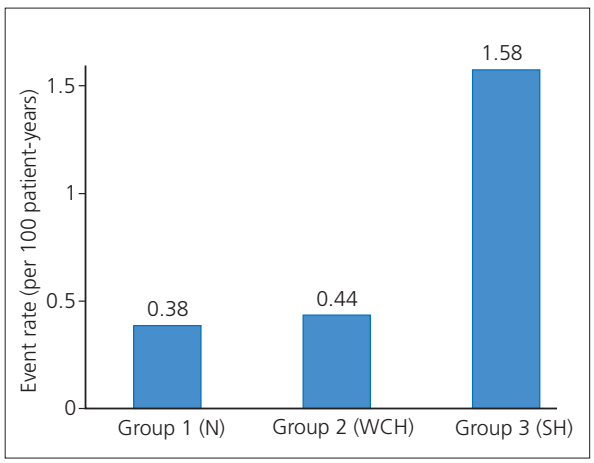


Fig. 1.2 Cardiovascular event rates in people with normal blood pressure (N), white-coat hypertension (WCH), and sustained hypertension (SH). (Adapted from Pierdomenico SD, Lapenna D, Di Mascio R *et al*. (2008) Short- and long-term risk of cardiovascular events in white-coat hypertension. *J Hum Hypertens* **22:**408–414.)

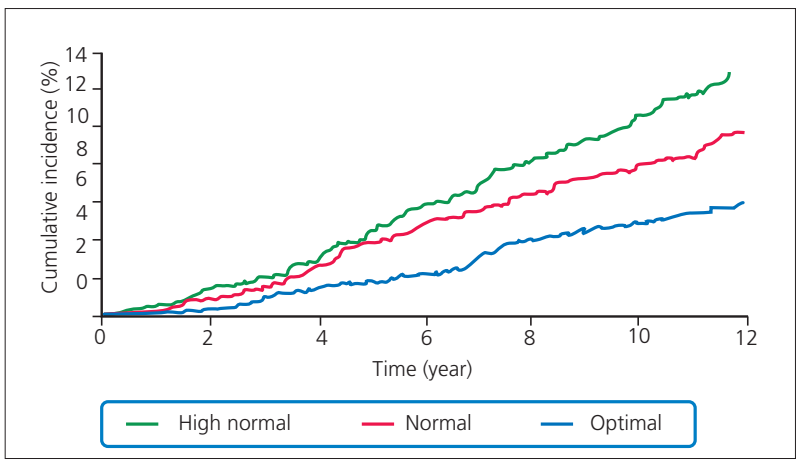


Fig. 1.3 Cardiovascular risk within the range of 'normal' blood pressure (from the Framingham Heart Study). (Adapted from Ramachandran SV, Larson MG, Leip EP *et al*. (2007) Impact of high-normal blood pressure on the risk of cardiovascular disease. *N Engl J Med* **345:**1291–1297.)

Risk of cardiovascular disease associated with hypertension

According to the Framingham Heart Study, hypertension in men is the primary cause of coronary heart disease that results in disability and death. In a global study of patients (both male and female) in over 50 countries, it was estimated that nearly 20% of the risk of the first myocardial infarction (MI) could be attributed entirely to hypertension. In women, mortality as a consequence of hypertension is more likely to be due to stroke. Indeed, hypertension is the most important risk factor for predicting ischemic stroke and intracerebral hemorrhage (Figures 1.4–1.7).

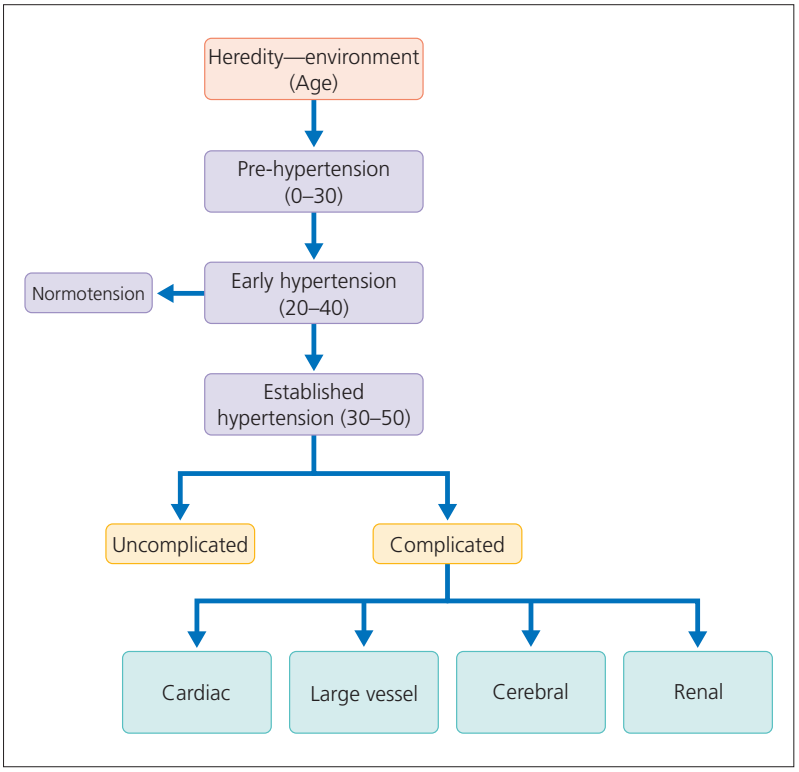


Fig. 1.4 Hypertension onset: progression and complications.

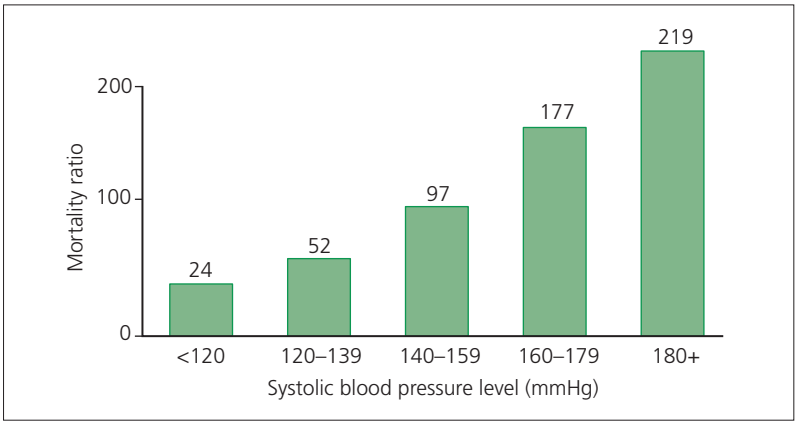


Fig. 1.5 Systolic blood pressure and morbitity (from the Framingham Heart Study). (Adapted from Dawber TR, Kannel WB, Revotskie N *et al*. (1962) The epidemiology of coronary heart disease – the Framingham enquiry. *Proc R Soc Medicine* (1962) **55:**265–271.)

Cardiovascular disease and prehypertension

Increased risk of CVD is not limited to patients who have hypertension by traditional definitions. The risk of developing CVD is related to the BP level (Figure 1.8). Studies of the population at large and patients with documented CVD suggest that this relationship begins at BP levels above 115/75 mmHg, which is considered

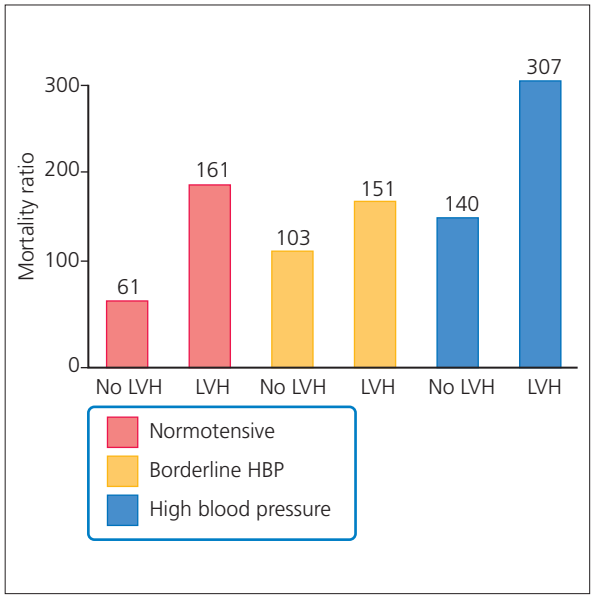


Fig. 1.6 Risk of developing chronic heart disease (from the Framingham Heart Study). (Adapted from Dawber TR, Kannel WB, Revotskie N *et al*. (1962) The epidemiology of coronary heart disease – the Framingham enquiry. *Proc R Soc Medicine* (1962) **55:**265–271.)

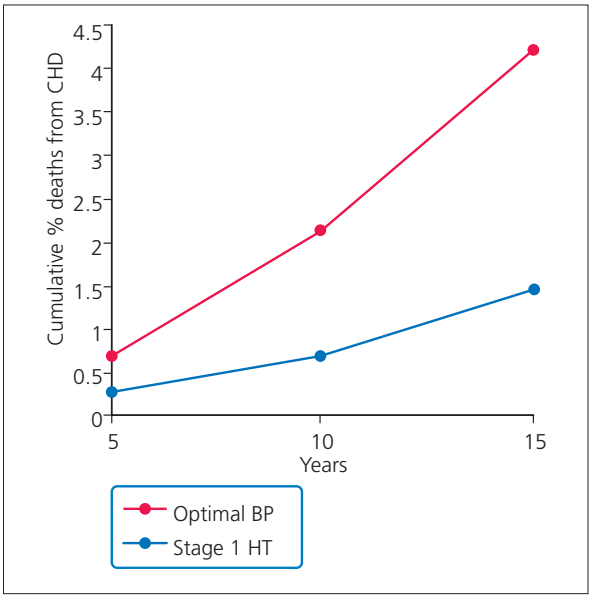


Fig. 1.7 Risk of chronic heart disease (from the Multiple Risk Factors Intervention Trial [MRFIT] cohort). (Adapted from Neaton JD, Kuller L, Stamler J *et al*. (1995) Impact of systolic and diastolic blood pressure on cardiovascular mortality. In: *Hypertension: Pathophysiology, Diagnosis, and Management*. (eds JH Laragh, BR Brenner) Raven Press, New York, pp. 127–144.)

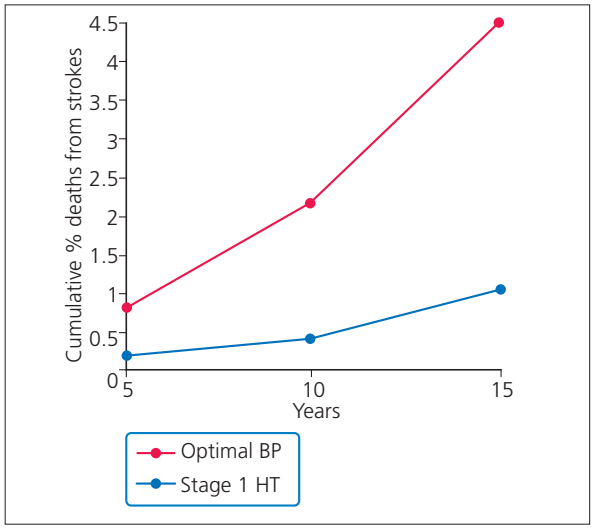


Fig. 1.8 Risk of stroke mortality (from the Multiple Risk Factors Intervention Trial [MRFIT] cohort). (Adapted from Neaton JD, Kuller L, Stamler J *et al*. (1995) Impact of systolic and diastolic blood pressure on cardiovascular mortality. In: *Hypertension: Pathophysiology, Diagnosis, and Management*. (eds JH Laragh, BR Brenner) Raven Press, New York, pp. 127–144.)

'normal' BP. This range of BP levels between normal patients (120/80 mmHg) and hypertensive patients (140/90 mmHg) is referred to as prehypertension, and patients with BP levels within this range have an increased risk of developing coronary heart disease or having a MI compared with patients with a normal BP. A study limited to women also suggests that having a stroke is more likely in the prehypertension population than in the population with normal BP. However, direct conclusions from these data are complex because prehypertensive patients also tend to have additional CVD risk factors compared with patients with normal BP. These risk factors include increased body weight, elevated serum cholesterol level and diabetes mellitus, which add to the difficuty in determining cause and effect relationships. The best evidence for a relationship between increased BP at prehypertension levels and CVD is supported by outcomes from antihypertensive therapy. Treatment with antihypertensive drugs decreases the risk of developing CVD by about two-thirds compared with untreated patients, even when other risk factors remain unchanged.

Changes associated with hypertension that can lead to cardiovascular disease

Diseases of the CV system that are associated with hypertension can be attributed, at least in part, to changes in organ systems as the body attempts to adapt to higher arterial pressures. Elevated BP leads to structural changes in the arterioles and the remainder of the vascular tree, referred to as remodeling or hypertrophy, which contribute to damage to other organ systems. Larger vessels undergo arteriosclerosis in response to the higher sheer stress imposed by hypertension. This correlates with patient age, with older patients having a higher relative risk of arteriosclerosis than younger patients. Hypertension also plays an independent role in atherosclerosis, causing substantial premature morbidity and mortality. When these changes occur in cerebral blood vessels, the risk of stroke is increased.

A common abnormality seen in hypertensive patients is left ventricular hypertrophy (LVH), which occurs as a result of thickening in the left ventricular, changes in left ventricular geometry, and an increase in left ventricular mass. LVH is a precursor of heart failure, MI, and cardiac arrhythmias. The majority of patients with CHF have a history of chronic hypertension, with the risk for CHF increased by three times in hypertensive patients compared with people with normal BP levels.

Prevalence and epidemiology of hypertension

Hypertension in the population

Hypertension and its associated complications affect a large number of people around the world. A recent National Health and Nutrition Examination Survey (NHANES) estimated that 29–32% of the adult population (age >18 years) in the USA could currently be classified as having hypertension (systolic BP >140 mmHg

or diastolic BP >90 mmHg). This prevalence equates to over 60 million people. Perhaps even significant is the finding that an additional 28% of the population has prehypertension. Thus, the majority of the population of the USA has one of the major risk factors for CVD. Global statistics are similar. Currently, 26% of the world population is estimated to have this hypertension, which translates to almost one billion people with this disease.

In a recent review studying the worldwide prevalence of hypertension (Figure 1.9), the lowest prevalence was found in rural India (3.4% in men and 6.8% in women) and the highest prevalence was in Poland (68.9% in men and 72.5% in women). Awareness of hypertension was reported in 46% of the populations studied, and varied from 25.2% in Korea to 75% in Barbados. Treatment frequently also varied greatly, ranging from 10.7% in Mexico to 66% in Barbados, and BP control (BP <140/90 mmHg while on antihypertensive medication) varied from 5.4% in Korea to 58% in Barbados.

Despite recent efforts to control hypertension, these statistics show little improvement in the USA. There has been no significant decrease in the percentage of the population with hypertension in recent decades.

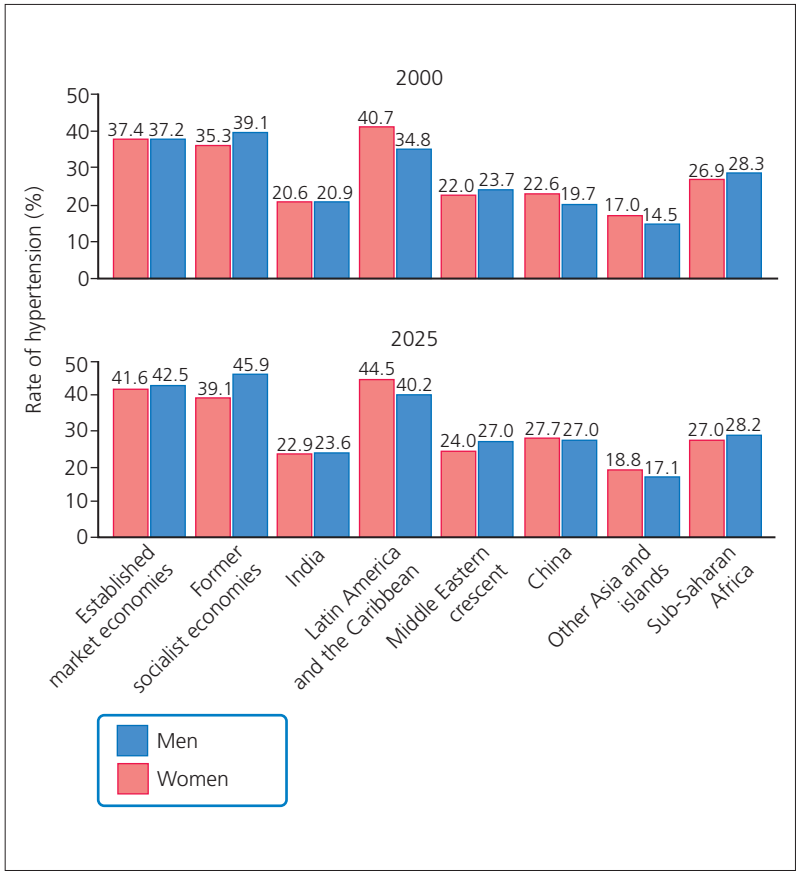


Fig. 1.9 Prevalence of hypertension in people aged 20 years and older by world region and sex in 2000 (upper) and projected for 2025 (lower). (Adapted from Kearney PM, Whelton M, Reynolds K *et al*. (2005) Global burden of hypertension: analysis of worldwide data. *Lancet* **365:**217–223.)

These data have been examined and sorted into different subgroups to try to identify subpopulations that may be at increased risk (*Table 1.2*). As BP tends to rise with aging, it is not surprising that the majority of adults over 60 year of age have hypertension (67%), compared with just 7% of 18–39 year olds and 31% of 40–59 year olds. The prevalence in men and women was found to be statistically similar, with nearly 30% of both genders having hypertension. Ethnic breakdown showed more diversity, with non-Hispanic blacks having the highest prevalence of hypertension in the population (almost twice the prevalence in Mexican Americans).

In people with prehypertension (*Table 1.3*), men are significantly more likely to have prehypertension than women (34% and 22%, respectively). Ethnic subgroups are not as dispersed, ranging from 27 to 31% with prehypertension. Mexican Americans are significantly more likely to have prehypertension than non-Hispanics. Analysis by age shows that 40–59-year-old people have the highest prevalence of prehypertension (34%), followed by people aged 18–39 years old (29%). Only 18% of individuals aged 60 years or older have prehypertension. This is not surprising as the majority of the population aged 60 years and older already have BPs in the hypertensive range. These data in the older population are supported by the observations from the Framingham Heart Study (FHS), which

Table 1.2. Prevalence of hypertension in subgroups of the adult population in the USA. (From National Health and Nutrition Examination Survey, 2005–2006.)

Gender	Prevalence (%)	Age	Prevalence (%)	Race	Prevalence (%)
Men	32	18–39	7	Mexican American	22
Women	29	40–59	34	Non-Hispanic black	41
		60 +	67	Non-Hispanic white	28

Table 1.3. Prevalence of prehypertension in subgroups of the adult population in the USA. (From National Health and Nutrition Examination Survey, 2005–2006.)

Gender	Prevalence (%)	Age	Prevalence (%)	Race	Prevalence (%)
Men	34	18–39	29	Mexican American	31
Women	22	40–59	34	Non-Hispanic black	27
		60 +	18	Non-Hispanic white	29

determined the likelihood of a person developing hypertension based on starting BP and age. The study demonstrated that people aged 65 years or older are 1.5 to 3 times more likely to progress to hypertensive levels compared with those younger than 65 years. Furthermore, the FHS estimated that 55–65-year-old people had a greater than 90% chance of developing hypertension during their lifetime (Figure 1.5).

Increased risks of cardiovascular disease associated with hypertension (Figures 1.2, 1.3)

The risk of coronary heart disease, stroke, or cardiovascular mortality increases with a concurrent increase in BP, starting at 115/75 mmHg. This correlation appears to be true for patients being treated for hypertension and for those not being treated. Among patients who already have coronary heart disease, the risk also increases with rises in BP. A global study with a 25-year follow-up of 12,000 men aged 40–59 years in seven countries estimated that the relative risk of death increased 1.28-fold for every 10 mmHg increase in systolic BP. The risk of death in hypertensive patients (at BPs of 140/85 mmHg) was three-fold higher in the USA and Northern Europe than in Japan and Southern Europe, most likely because of other contributing factors. These contributing factors, however, can often be modified in individual patients. It has been estimated that 68% of hypertensive patients take one or more antihypertensive medications and of these, 64% have BPs below 140/90 mmHg. There has not been any change in the total percentage of the population with hypertension in the USA, but many individual patients have had a reduced risk of CVD by adhering to physician-directed treatment.

The public health cost of hypertension: a global challenge

Several studies have estimated the costs of hypertension and the economic burden imposed by escalating BP levels in the community. This includes expenditure for hypertension treatment and care, plus the cost in life and loss of productivity. Additional studies have tried to determine the cost of treating prehypertensive patients or ineffective/incorrect treatment of patients. The chronic nature of hypertension, the large number of people with hypertension, and complications such as CVD and hypertension-related kidney failure make hypertension highly expensive to both individuals and society.

Financial burden of hypertension in the USA

An estimated 60 million Americans have hypertension, with almost 60 million more having prehypertension or non-optimal BP. The current cost estimates for treating hypertension range from 15 to 30 billion US dollars (USD) per year. The costs of treating medical conditions associated with hypertension are an additional 87 billion USD. This total includes 30 billion USD for CVD and 57 billion USD for all other conditions attributable to hypertension. Together, more than 100 billion USD are used to treat hypertension and related conditions, just less than

10% of the total healthcare costs in the USA. Prescription medications, inpatient treatment, and outpatient treatment account for 90% of the costs directly related to hypertension, with prescription medication alone accounting for one-half of the expenditure. Health preactitioners following established treatment protocols is important in helping control the costs of hypertension, as deviations from established protocols are estimated to cost an additional 13 billion USD annually. Almost 10% of this cost is caused by patients being given inappropriate prescriptions that are inconsistent with evidenced-based recommendations.

Global financial burden of hypertension

The total cost of hypertension has also been studied globally. These studies have taken into account costs associated with both hypertension and prehypertension. The International Society of Hypertension tried to quantify the cost of treating elevated BP and diseases related to elevated BP (including new cases of ischemic heart disease and stroke) and estimated that 370 billion USD was spent around the world in 2001 because of non-optimal BP levels. This global estimate suggests that the direct cost of non-optimal BP control accounts for about 10% of all healthcare expenditure. To put this into perspective, because the World Bank defines the world's poorest citizens as those living below 1 USD/day, a 370 billion USD expenditure could raise all of these one billion citizens out of extreme poverty, highlighting both the magnitude of the expense and the benefits that could be realized if hypertension could be eliminated.

Other costs of hypertension

There are also 'indirect costs' of hypertension, including loss of life and loss of productivity due to absenteeism, illness, and death. Globally, it has been estimated that hypertension accounts for 14% of deaths, and approximately 6% of disability-adjusted life years (a measure of work time lost to disability) can be attributed to non-optimal BP. Although such indirect costs are obviously substantial, their precise financial burden is difficult to estimate.

Total costs of hypertension

The total cost of hypertension, using direct costs (treatment of hypertension and related medical conditions) and indirect costs (loss of productivity and life), is estimated at a staggering four trillion USD globally. It is obvious that hypertension – both controlled and uncontrolled – is a costly and likely unstainable burden demanding much more attention than it currently receives.

CHAPTER 2

DIAGNOSIS AND EVALUATION OF HYPERTENSION

Overview

Care for patients with hypertension begins with identification of elevated BP. Healthcare providers should ensure that the proper techniques and equipment are used for the measurement of BP, as failure to follow correct protocols can lead to inaccurate measurements and misdiagnosis. Healthcare providers should also be aware of the difficulty in diagnosing hypertension based on a single clinic visit, as many external factors can contribute to 'artificially' abnormal BP readings. Only after hypertension has been correctly diagnosed should healthcare providers carry out a clinical search for causes of secondary hypertension, which may respond to definitive treatment. If no secondary causes are found, focus should shift to treatment of the hypertension *per se* in order to limit the risk of complications.

Classification of hypertension

In the USA, the most often used definition of hypertension comes from the Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The most recent JNC Guidelines (JNC-7) for hypertension were published in 2003. According to the JNC, normal BP is defined as systolic pressure less than 120 mmHg and diastolic pressure less than 80 mmHg (*Table 2.1*). Hypertension is defined as systolic pressure of 140 mmHg or higher and/or a diastolic pressure 90 mmHg or higher. Hypertension is further classified as stage 1 or stage 2 according to the BP. BP levels greater than normal but below the hypertension cut-off are called prehypertension.

The JNC-7 Guidelines lowered the levels that are defined as normal BP compared with the previous report (JNC-6). This reflects current evidence that BP levels of 115/75 mmHg or greater contribute to cardiovascular risk. The terminology is also different: JNC-6 Guidelines used 'optimal', 'normal', and 'high normal' to describe patients who were not hypertensive. In JNC-7, normal levels are lower than 120/80 mmHg, whereas JNC-6 defines this as optimal, with normal classified as 120–129 systolic and 80–84 diastolic. In both reports, the definition of hypertension was the same: 140/90 mmHg or above. JNC-6 definitions for classification of patients are no longer recommended, although because many long-term epidemiology studies still use the JNC-6 Guidelines, knowledge of this older set of guidelines is useful for understanding these studies.

Table 2.1. JNC-7: Classification of blood pressure into hypertension categories.

		Systolic (mmHg)	Diastolic (mmHg)
Normal		Below 120	Below 80
Prehypertension		120–139	80–89
Hypertension	Stage 1	140–159	90–99
	Stage 2	160 and above	100 and above

Table 2.2. ESH/ESC Guidelines 2013: Definitions and classification of office blood pressure levels.

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension	≥140	and	<90
The BP category is defined by the highest level of pressure, whether systolic or diastolic. Isolated systolic hypertension should be graded 1, 2, or 3 according to systolic BP values in the ranges indicated.			

Awareness of the JNC-7 Guidelines is also useful for comparison with hypertension in other parts of the world. In 2013, the European Societies of Hypertension and Cardiology published recommendations for classification of BP (*Table 2.2*). These guidelines use the same classifications for non-hypertensive patients as JNC-7 and the same starting BP levels to define hypertensive patients, but they define three stages of hypertension (*Table 2.2*): stage 1 (140–159/90–99 mmHg); stage 2 (160–179 mmHg/100–109 mmHg); stage 3 (patients with BP levels higher than 180/110 mmHg)).

Measurement of blood pressure and diagnosis

Healthcare professionals routinely check BP during clinic visits. The timing, interval, and number of these measurements vary depending on numerous factors and there is no known optimal interval for screening individual patients. The US Preventative Service Task Force has made recommendations based on the last known BP of a patient and recommends a BP check every two years for those with normal BP and yearly BP measurements for prehypertensive patients.

Equipment used for blood pressure measurements

Auscultation of the Korotkoff sounds using a sphygmomanometer remains the most common method for checking BPs during clinic visits. Mercury sphygmomanometers are most accurate, but due to cost and the potential chemical hazards of mercury, aneroid gauges are more often used. For accuracy, aneroid devices should be calibrated every six months against a mercury-containing sphygmomanometer. Therefore, alternative devices, which rely on an automated oscillometer, are being increasingly used for BP measurement in clinics and at home. Automated methods have the advantage of reduced operator error and they require less training. However, automated oscillometers have greater inherent errors and are considered inaccurate for careful BP measurement. Oscillometers also generally record lower BP values for a patient compared with a sphygmomanometer, making comparison between the methods more difficult.

Using a correct cuff size is crucial for accurate BP measurements. The bladder contained in the cuff should be long enough to cover 80% of the circumference of the patient's upper arm and the cuff width should be 40% of the length of upper arm. The center of the bladder should be placed over the brachial arterial pulse. If these criteria are not met, the pressure generated by the air bladder may not be correctly transmitted to the brachial artery. A bladder that is too short can lead to overestimation of BP, up to 50 mmHg in obese patients, while bladders that are too wide cause readings that are too low. Cuff sizes to be used, based on arm circumference, are listed in *Table 2.3*.

Table 2.3. Correct cuff sizes for different arm circumferences.

Arm circumference	Cuff name	Cuff size
22–26 cm	Small adult	12 x 22 cm
27–32 cm	Adult	16 x 30 cm
35–44 cm	Large adult	16 x 36 cm
45–52 cm	Adult thigh	16 x 42 cm

Technique for blood pressure measurements

The technique used to measure BP is important in order to ensure accurate detection and diagnosis of hypertension, which is especially true during the initial visit by the patient to the clinic. Whether the BP differs between the two arms is important because in just over one-third of patients the systolic pressure may differ by at least 10 mmHg. The arm that displays the higher pressure should be used for further measurements. BP may also vary with postural changes. Generally, the systolic pressure will decrease and the diastolic pressure will increase a few mmHg as a patient stands. Elderly people can be overly sensitive to standing, with 10% of those over the age of 65 years having a drop of 20 mmHg upon standing. BP should be taken after sitting quietly for five minutes, immediately after standing, and two minutes after standing. If these measurements differ by only a few mmHg, BPs may be taken only while the patient is seated duing follow-up examinations.

Physicians should ascertain if a patient has recently (within one hour) exercised or consumed nicotine, caffeine, or alcohol, as all of these substances can affect BP. Patients should also be relaxed before measuring BP, since stress or activity can cause higher BPs. The patient should be seated for five minutes before measurement and should not speak or move during the measurement.

The BP cuff should be placed around the upper arm such that the edge of the cuff is 2.5 cm (1 in) from the antecubital space. It does not matter if this is over the bare arm or over a single shirt sleeve. The cuff should be at heart level. If the arm is allowed to hang, the cuff could be as much as 15 cm (6 in) below the level of the heart, which could increase the BP by 10–15 mmHg because of hydrostatic pressure due to gravity. The stethoscope should not be used in such a way that it applies excess pressure to the arm. The bell of the stethoscope is recommended rather than the diaphragm, which could increase the delay in hearing the pulsation and result in underestimation of diastolic pressure by as much as 15 mmHg.

The cuff should be inflated to a pressure approximately 30 mmHg above the estimated systolic pressure and then deflated at a rate of 2–3 mmHg per heartbeat. The systolic pressure occurs when the pulse can be felt in the brachial artery as the blood re-enters the artery. Using auscultation, this is the point where the pulse is first heard and is termed the Korotkoff phase 1 sound. The pulse will continue to be heard as the cuff is deflated. At a pressure of 8–10 mmHg above the diastolic pressure, the sound often becomes muffled (Korotkoff phase IV) and then pulse sounds will cease (Korotkoff phase V). The diastolic pressure is recorded as the point at which the pulse sounds end, unless the spread between Korotkoff phases IV and V is more than 10 mmHg, in which case the phase IV point is recorded as the diastolic pressure.

Diagnosis of hypertension

The diagnosis of hypertension should not made on a single measurement of BP at the first clinic visit. There are many factors that can influence BP (see below). Even if all extraneous factors can be controlled, BP measurements vary with time of day, season of year, stress, and many other factors. On average, the BP of a patient will drop 10–15 mmHg between the first visit to a new physician and the third visit to the same physician. Patients with mild hypertension may require as many as six visits before a stable, baseline value can be established. Accurate diagnosis of mild hypertension can be made only after at least three to six separate BP measurements performed over weeks or even months.

Blood pressure measurement outside the clinic

One strategy to overcome some of the limitations of measuring BP at the clinic is to have patients obtain out-of-clinic measurements, since these are not subject to the effects of stress during visits to the clinic. Also, many more measurements are performed over a short period of time, which can be averaged to help control for biological variability (Figure 2.1) Out-of-clinic measurements include home-based measurements as well as ambulatory BP monitoring (ABPM). Generally, these systems are set up by the physician's clinic. In a home measurement, the patient is responsible for tracking the BP. The addition of home measurement to monitoring based on clinic measurements has been recommended by numerous guidelines around the world.

The 2011 UK National Institute for Health and Care Excellence (NICE) Guidelines recommend that a diagnosis of primary hypertension should be confirmed using 24-hour ABPM or home BP monitoring (HBPM), rather than be based solely on measurements of BP taken in the clinic. This new recommendation is a clear departure from the earlier 2006 Guidelines and primarily draws on substantial new evidence that ABPM is more accurate than clinic and home monitoring in defining the presence of hypertension, with the objective that implementation of a diagnostic strategy for hypertension using ambulatory monitoring following an initial raised clinic reading would reduce misdiagnoses and would be appropriately cost-effective.

ABPM uses an automated device to measure BP throughout the day, with measurements made at set times, such as every half hour, to provide a more detailed view of BP changes in a 24-hour period. ABPM and home monitoring provide a better prediction of risk compared with clinic-based measurements alone.

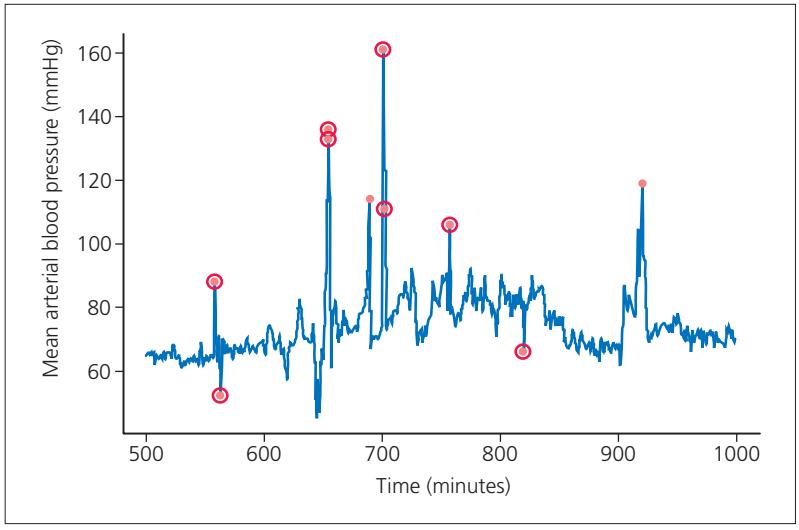


Fig. 2.1 Variability of blood pressure levels on ambulatory blood pressure recording.

Table 2.4. Illustrative examples of possible discrepancies in the measurement of blood pressure.

BP measurement method	Threshold for stage 1 hypertension	Threshold for stage 2 hypertension
Clinic BP reading	140/90 mm Hg	160/100 mm Hg
Ambulatory BP reading	135/85 mm Hg	150/95 mm Hg

The 2011 NICE Guidelines (see *Table 2.1*) also provide a revised algorithmic approach to the diagnosis of hypertension. Because this Guideline update recommends using the ABPM daytime average BP (calculated using a minimum of 14 daytime measurements) to confirm a diagnosis of hypertension for initiating treatment, it was necessary to define the ABPM daytime average pressures that are equivalent to the thresholds for stage 1 and stage 2 hypertension, previously defined according to clinic BP readings alone (*Table 2.4*).

Factors affecting blood pressure measurement

Variability of blood pressure

BP measurements often differ between clinic visits for many reasons, including differing techniques and devices, and measurement error. In addition, BP changes throughout the day depending on activity and stress levels, biological variations, and other changes within the patient. Increased physical and mental activity cause an increase in BP and a relaxed mood causes BP to fall. BP will decrease by as much as 15% during sleep. Respiration and heart rate also contribute to fluctuations in BP, and caffeine, nicotine, and alcohol consumption can all cause increased BP over short periods of time (i.e. minutes to an hour).

White-coat hypertension

Visits to physicians' clinics are stressful for many people. Such stress is the basis for the recommendation that mild hypertension should not be diagnosed until after multiple clinic visits when seeing a new physician. A subset of patients is so bothered by a consultation with healthcare providers that their BP is elevated sufficiently in the clinical setting to give readings that would signal hypertension, while their BPs are not at hypertension levels outside the clinic. These patients are designated as having 'white-coat' hypertension (Figures 2.2 and 2.3). Diagnosis of white-coat hypertension is based on clinic-obtained BP measurements of 140/90 mmHg or above when out-of-clinic measurements are less than 135/85 mmHg. White-coat hypertension, however, is not innocuous, as it is associated with cardiovascular risk (Figure 2.4).

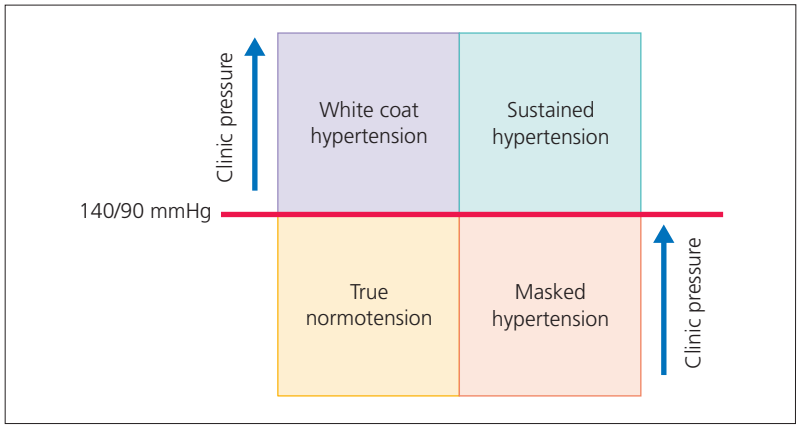


Fig. 2.2 Types of blood pressure changes in the clinic.

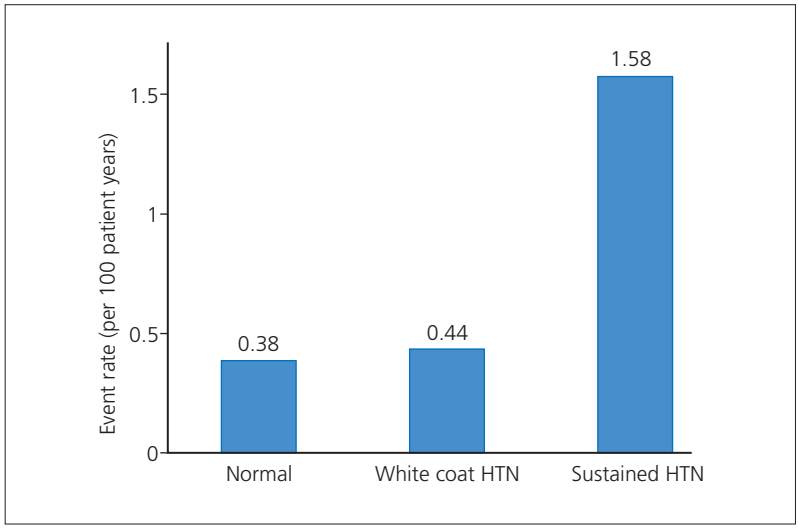


Fig. 2.3 Cardiovascular event rate in variable forms of hypertension. (Adapted from Pierdomenico SD, Lapenna D, Di Mascia R *et al*. (2008) Short- and long-term risk of cardiovascular events in white-coat hypertension. *J Hum Hypertens* **22:**408–414.)

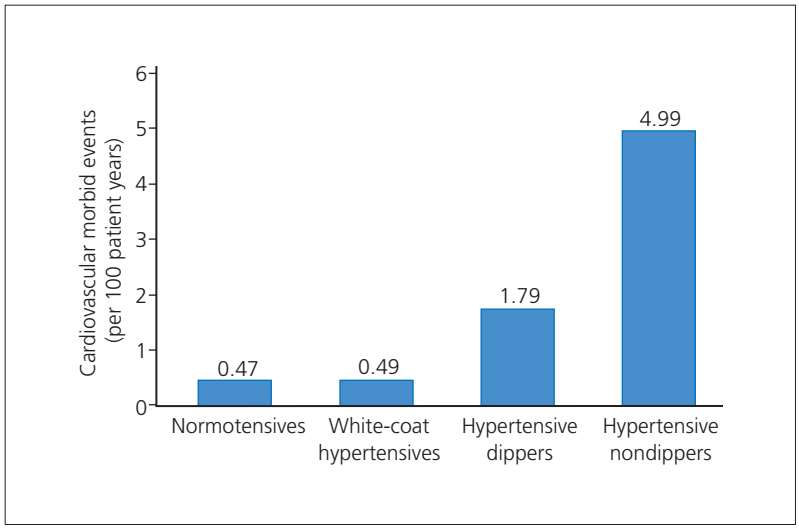


Fig. 2.4 Incidence of cardiovascular complications in four forms of hypertension. (Adapted from Verdecchia P, Porcellati C, Schillaci G *et al*. (1994) Ambulatory blood pressure. An independent predictor of prognosis in essential hypertension. *Hypertension* **24:**793–801.)

White-coat hypertension is estimated to affect at least 10% of the population, with some estimates suggesting a prevalence of greater than 20% of the population. The condition generally occurs in patients with mild hypertension and is most often seen in the young or in the elderly and is least common in middle-aged adults.

White-coat hypertension contributes to resistant (or refractory) hypertension, which occurs in a small subset of hypertensive patients who do not show a satisfactory reduction of BP even under treatment with a combination of three different hypertension medications. In many cases, resistant hypertension is a result of pseudoresistance. In patients with pseudoresistance the BP appears to be elevated because of circumstances that lead to inaccurate measurements. Having a nurse or a technician measure the BP, rather thn a physician, may improve the BP, but the best way to determine if white-coat hypertension is present is with ABPM.

Evaluation of patients with hypertension

When a patient is initially diagnosed with hypertension, an evaluation must be perfomed to determine the most appropriate treatment. There is a possibility of some TOD, which might be indicated by factors such as headaches, chest pain, or dyspnea. Kidney disease is a common problem associated with hypertension and should be considered when deciding a treatment course. Possible TOD can be uncovered during physical examination and from the patient's history. Because hypertension is a known risk factor for CVD, overall cardiovascular risk must be assessed. The examiner should also be alert to factors that may aggravate hypertension. For example, medications (prescription or non-prescription) may cause increased BP, as can alcohol, excess sodium ingestion, and tobacco use. Although extensive testing is often not cost-effective. a minumum evaluation should consist of a urinalysis, blood count, fasting lipid profile, electrocardiogram, and routine blood chemistries.

Finally, asessment should include a determination whether hypertension is secondary to some other condition that needs treatment. In these cases, if the primary condition can be cured, the hypertension will also be resolved. For example, alcohol use of greater than two ounces (56.7 grams) a day is the most curable condition that leads to mild hypertension. Physicians must use patient history and a physical examination to determine if additional testing is warranted to detect possible secondary hypertension. Measurement of microalbumin levels is useful for detecting nephropathy, although microalbumin is an early risk marker for hypertension even in the absence of kidney dysfunction. Renovascular hypertension (RVHT) is another common correctable cause of secondary hypertension. It is not usually associated with mild hypertension (less than 1% of cases); however, it is often a cause of severe hypertension (up to 45% of patients). Other suspected causes of secondary hypertension can be tested for depending on initial findings in the evaluation.

CHAPTER 3

PRIMARY OR SECONDARY HYPERTENSION

Overview

The majority of patients with hypertension have *primary* (or *essential*) hypertension. The pathogenesis of primary hypertension is not completely understood; at best, it is known that there are risk factors and conditions that may contribute to development of primary hypertension. This lack of understanding precludes a true cure of primary hypertension. Rather, the clinician is limited to reducing the patient's BP to goal values through lifestyle modification and prescribing antihypertensive medications. With this approach, BP can often be reduced to normotensive levels. In the majority of cases, the only treatment is long-term BP control.

In some patients, hypertension may be secondary to other, coexisting conditions, and in these cases the cause of the hypertension is better understood. Usually, the elevated BP can be resolved or improved with correction to the underlying condition, and this becomes the focus of treatment. Approximately 5% of patients with hypertension have a secondary form of hypertension.

Determinants of blood pressure

The BP is determined by a combination of factors, including CO, total body fluid volume, and resistance of blood moving through the arterial system. In addition, many environmental factors alter the function of organ systems, thereby generating a complex interaction of multiple factors, all adding to the difficulty in determining the cause(s) of primary hypertension.

Cardiac output and blood volume

CO is the amount of blood pumped by the heart over a period of time and is determined by the speed at which the heart beats (heart rate) and the amount of blood pumped by each heart beat (stroke volume). Left ventricular stroke volume is the difference between the volume of blood that has filled the left ventricle at

the end of diastole (end diastolic volume, EDV) and the amount of blood left in the left ventricle immediately following systolic contraction (end systolic volume, ESV). Stroke volume is dependent on the *preload*, the *afterload*, and the *contractility* of the heart:

- Preload is the amount of stretch of the cardiac muscle due to blood filling the heart, which is controlloed by the EDV filled by venous return from circulation. Any factor that alters the returning volume will alter the EDV and the preload. Changes in the EDV affect the stroke volume and, ultimately, CO. A more rapid heart rate, for example, diminishes the amount of blood filling the ventricles and thus decreases preload.
- Afterload is back pressure from the arteries near the heart because of blood movement. Afterload is relatively constant and does not normally make a large contribution to changes in stroke volume. In patients with hypertension, however, afterload is more important, as elevated BP reduces the amount of blood ejected from the heart with each heart contraction. This leaves more blood in the heart after each contraction, raising the ESV and thus reducing the stroke volume.
- An extrinsic factor affecting stroke volume is cardiac contractility. Cardiac contractility is termed extrinsic because it does not depend on myocardial stretch. Increased contractility increases the force and amount of blood ejected with each heart beat. This reduces the ESV, increasing the stroke volume. Contractility is increased due to cytosolic increase in calcium ions prior to contraction.

The components that regulate CO rely on a number of sensors sensitive to hemodynamic changes including baroreceptors and chemoreceptors located within arteries and receptors in skeletal muscle that sense contractions. Baroreceptors are mechanoreceptors that sense changes in vessel wall stretch and produce a rapid response to alterations in BP. They act as a buffering system to moderate normal short-term changes in BP. In hypertension, the increased stretching of arterial walls activates these receptors, causing inhibition of the vasomotor center and resultant reduction in heart rate (to lower CO) and vasodilation (to decrease SVR). These changes reduce the BP. If the BP is too low, these receptors sense the reduction in arterial pressure and increase the CO and stimulate vasoconstriction. The long-term function of baroreceptors is not known. Baroreceptors can be reset and may no longer respond to changes in stretching associated with increased BP, which may occur in hypertension.

Blood volume is another important factor in BP level. Regulation of blood volume is a long-term modulator of CO. Blood volume influences venous pressure and ventricular filling, which causes changes in EDV and stroke volume. BP is directly tied to blood volume; when blood volume increases, BP rises.

The kidneys have an important role in controlling blood and fluid volume. They can directly alter blood volume by increasing the filtration of fluid and reducing sodium retention and the fluid that accompanies it. Indirectly, the kidneys can regulate the renin–angiotensin–aldosterone system (RAAS) to change BP and ultimately increase the blood volume.

Table 3.1. A partial list of mechanisms that can influence cardiac output or systemic vascular resistance. This list only includes a few neurotransmitters and hormonal signaling molecules.

- Norepinephrine/epinephrine
- Angiotensin II
- Endothelin
- Nitric oxide
- Atrial natriuretic peptide/brain natriuretic peptide
- Acetylcholine
- Prostaglandins
- Aldosterone
- Bradykinin
- Vasopressin

Systemic vascular resistance

SVR is the resistance to blood flow in the arterial tree. Arteries are composed of endothelial cells, vascular smooth muscle cells, and connective tissue. The intrinsic myogenic tone of the vascular smooth muscle and the sympathetic nervous system (SNS) control the diameter of the vessel, which influences the SVR. The nervous system and the endothelial cells play a major role in modifying smooth muscle cell tone. (See *Table 3.1* for a partial list of factors that can alter SVR and CO.)

There are several vasodilators that reduce SVR, notably nitric oxide. Nitric oxide activates guanylate cyclase in smooth muscle cells, resulting in an increase in cyclic guanosine monophosphate (GMP) and vessel relaxation. Constriction of smooth muscle cells, however, increases SVR. This system prevents BP from falling too low and increases BP in response to stress or activity. Principal vasoconstrictors are angiotensin (AT) II (produced in response to release of renin by the kidney) and endothelin-1 (ET-1) produced by endothelial cells. ET-1 binds to receptors of vascular smooth muscle cells to activate voltage-dependent calcium channels. AT II binds to the G-protein coupled receptor AT_1 to increase cytoplasmic calcium concentrations.

Blood pressure regulation

Many physiological systems alter CO and SVR and thus regulate BP. Systemic and local hormones, metabolites, and neurotransmitters all contribute to signaling pathways that affect CO and SVR. The SNS and the RAAS play a particularly important role in BP management.

Sympathetic nervous system

The SNS can alter SVR and CO and thus regulate BP in response to stimuli (Figures 3.1 and 3.2). The parasympathetic nervous system mostly functions to downregulate the system and the main parasympathetic neurotransmitter, acetylcholine, is responsible for reducing heart rate. The SNS counteracts the relaxed state that dominates under parasympathetic activity to prepare the body for activity or stress. It is the SNS, through its main neurotransmitter, epinephrine, that results in many of the changes leading to increases in BP and, as such, it is an important target in treating hypertension.

The SNS signals via adrenergic receptors, which respond to the neurotransmitter norepinephrine (NE) (and epinephrine). Both alpha- and beta-adrenergic receptors, and several subclasses of each receptor, are involved. Alpha1, alpha2, and beta1 adrenergic receptors are the most important receptors in increasing and regulating BP. Stimulation of postsynaptic alpha1 and alpha2 adrenergic receptors located

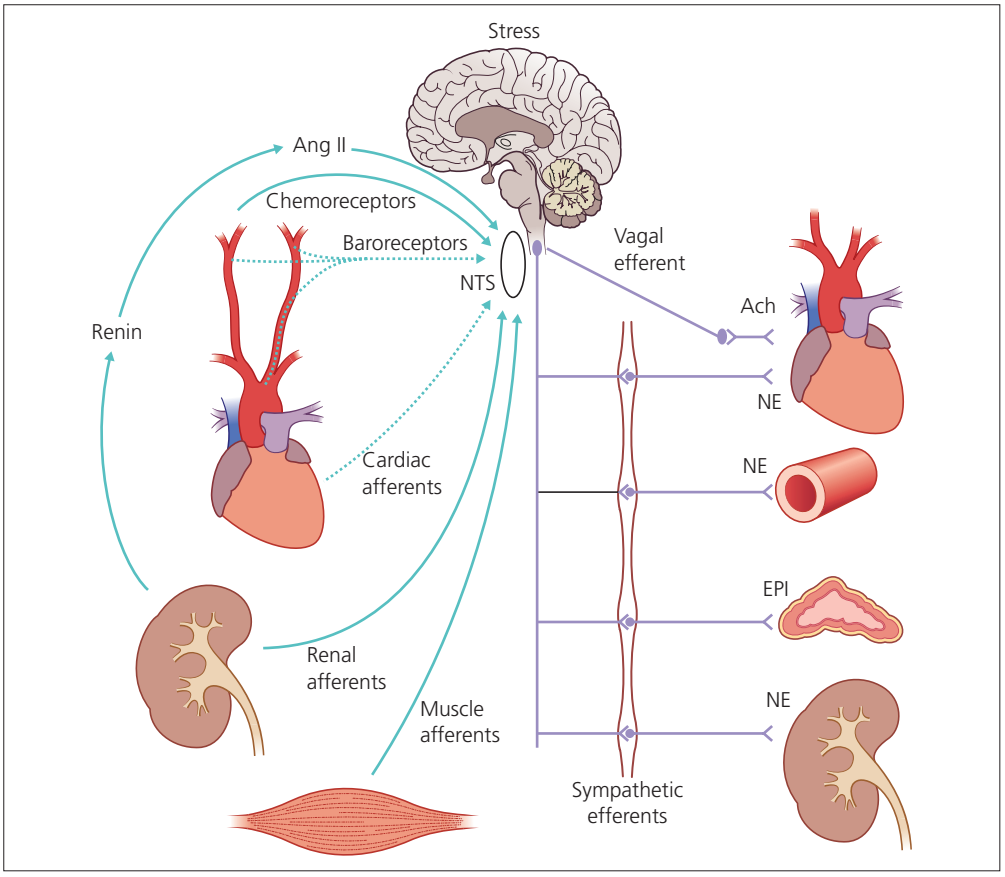


Fig. 3.1 Sympathetic nervous system and blood pressure regulation pathways.

on smooth muscle cells causes vasoconstriction of the vessels. Activation of beta1 adrenergic receptors in heart muscle causes increased heart rate and increases the amount of calcium in the muscle cells, thereby increasing cardiac contractility. CO is raised due to increased stroke volume and heart rate. Beta1 adrenergic receptors within the kidney, when stimulated, signal for release of renin, resulting in the production of the vasoconstrictor AT II. This stimulation of the SNS increases CO and SVR, leading to increased BP.

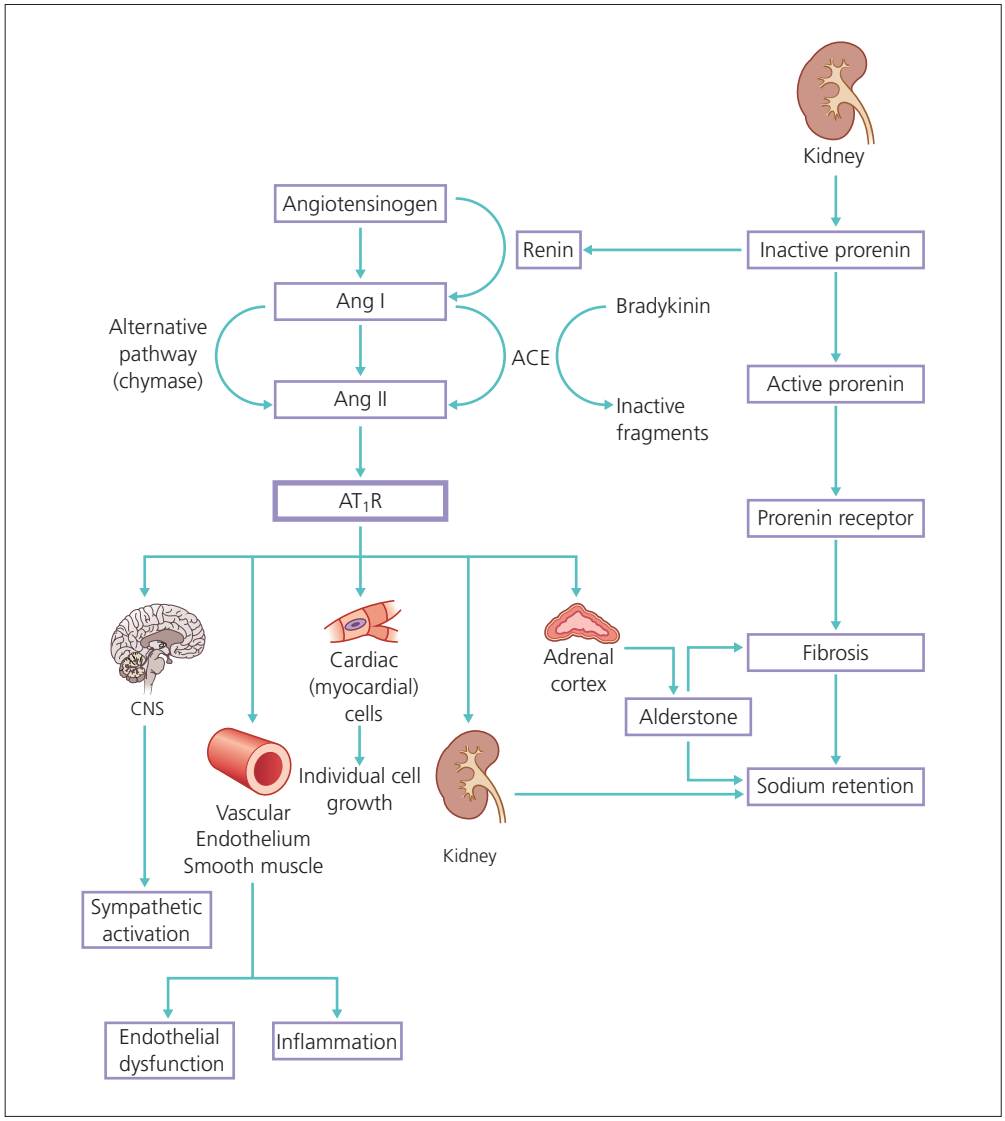


Fig. 3.2 Pathological consequences of activation of the renin–angiotensin–aldosterone system.

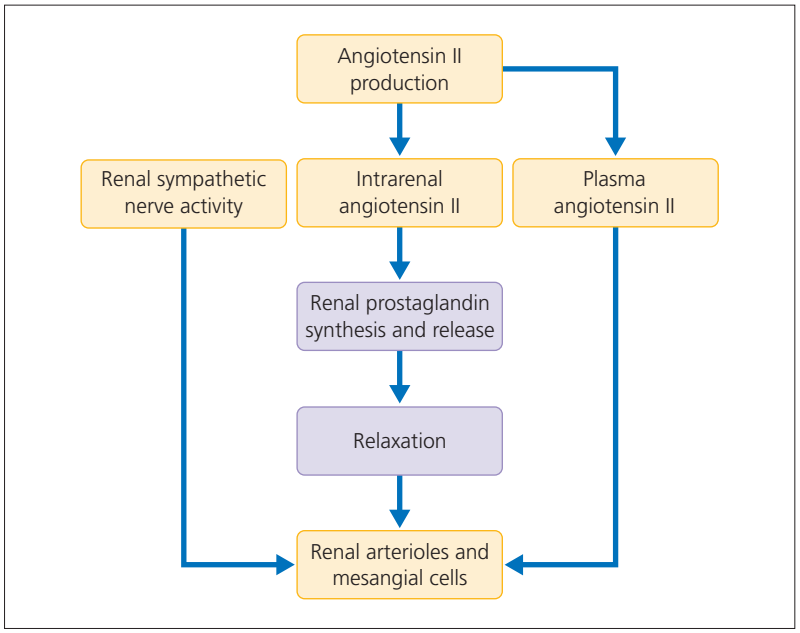


Fig. 3.3 Interaction between the renin–angiotensin–aldosterone system and the sympathetic nervous system at the kidney.

Renin–angiotensin–aldosterone system

Blood and fluid volume influence CO and are dependent on sodium regulation by the kidneys (Figure 3.3). The kidneys play a key role in controlling BP by causing changes in fluid volume, sodium homeostasis, and SVR. There are many different systems that regulate these factors, including the RAAS. This is a hormonal system that works to regulate BP and fluid volume through several mechanisms. In response to decreased blood fluid volume, the kidneys release the proteolytic enzyme renin into circulation. Renin cleaves angiotensinogen in the blood stream into AT I. AT I is further processed into AT II by angiotensin-converting enzyme (ACE). AT II is an active molecule and can stimulate two subtypes of receptors. Stimulation of the AT_1 receptor subclass can cause several changes that counteract low fluid levels and, in turn, increase BP. The first mechanism to increase blood fluid volume is through sodium retention. The AT II–AT_1 receptor pathway acts directly on the proximal renal tube and causes sodium reabsorption. AT_1 receptor activation also stimulates aldosterone release, causing further salt retention by the kidney. Both of these mechanisms lead to fluid retention and increased BP. AT_1 receptor stimulation causes changes in blood vessels via vasoconstriction. AT II, signaling through AT_1 receptors, is known to stimulate the SNS. This leads to changes in CO and SVR. All of these functions of AT II stimulation of the AT_1 subclass of receptors lead to an increase in systemic BP.

Primary hypertension: risk factors and blood pressure regulation

Although the cause of primary hypertension is unknown, there are many risk factors associated with hypertension. Children with hypertensive parents are more than twice as likely to develop hypertension, suggesting that there is a genetic component. This is supported by epidemiological evidence suggesting that up to 30% of BP

variation in the overall population is due to genetic abnormalities. Hypertension is also more prevalent in the USA in the non-Hispanic black population compared with the non-Hispanic white or Mexican American population. Hypertension as a whole is more severe in the black population compared with other races.

There are also many factors associated with lifestyle and environment that may contribute to an increased risk of developing hypertension (*Table 3.2*). Diet can enhance the susceptibility to develop, and once developed, sustain hypertension. For example, excess sodium intake and alcohol have both been linked to an increased likelihood of hypertension. Obesity is also a major risk factor, and in the elderly it is the main risk factor associated with the onset of hypertension. Psychological stress and lack of physical activity are also linked with elevated BP. While it is likely that all of these risk factors contribute to hypertension, the contribution of each risk factor depends on individual patient susceptibility.

Obesity and primary hypertension

Obesity is one of the main predictors of hypertension. The FHS looked at members of the population who were either overweight or obese and found that 25% had BP that was classified as hypertension. Being overweight also puts a person at increased risk of developing other risk factors associated with hypertension, including CVD and LVH. Obesity also increases low-density lipoprotein cholesterol, lowers high-density lipoprotein cholesterol, reduces glucose tolerance, and increases insulin resistance, all of which contribute to an increased risk of high BP.

Obesity can cause hypertension through several mechanisms. Activity of the RAAS is increased in overweight persons, leading to vasoconstriction and increased SVR. In addition to changes in hormonal systems, there are several metabolic changes caused by obesity. Insulin resistance, glucose tolerance, and dyslipidemia all lead to metabolic changes that contribute to elevated BP. Finally, obesity can increase the frequency of obstructive sleep apnoea, a condition associated with secondary hypertension.

Sodium intake and primary hypertension

Sodium balance correlates with raised BP. Primary hypertension is more common in populations that consume higher amounts of sodium, especially if the average sodium intake is 100 mEq/day or more, but it is rare in populations that consume less than an average of 50 mEq/day. Reducing sodium intake can have a beneficial effect on BP. Sodium reduction from 170–100 mEq/day can reduce systolic BP

Table 3.2. Some of the factors that may influence the development of primary hypertension.

- Increased sodium intake
- Increased body mass
- Increased alcohol intake
- Increased psychological stress
- Decreased physical activity
- Genetic predisposition
- Reduced potassium intake
- Reduced calcium intake

by 5 mmHg and diastolic BP by 3 mmHg on average. JNC 7 recommends that all persons with a sodium intake of 100–150 mEq/day should reduce their sodium intake to less than 100 mEq/day.

Changes in BP due to excess sodium intake reflect sodium sensitivity. Sodium sensitivity varies among individuals, and it increases with age or obesity. Non-Hispanic blacks are also more susceptible to sodium sensitivity and individuals with renal dysfunction have greater sodium sensitivity than people with normal kidney function. The relationship between sodium and BP is not ully understood, but may be related to fluid volume. Excess sodium intake requires the kidneys to filter more sodium out of the blood stream. If the level of sodium overwhelms the ability of the kidneys to filter sodium, sodium retention occurs, contributing directly to excess fluid volume and, ultimately, hypertension. It is also possible that excess sodium causes other changes in the body, such as activating signaling pathways, which can lead to inappropriate vasodilation or vasoconstriction. Sodium also exacerbates other risk factors such as microalbuminuria and dyslipidemia.

Genetics and primary hypertension

Many genes have been linked to hypertension (*Table 3.3*). One example of a single gene mutation leading to hypertension is Liddle's syndrome, caused by the dominant gain of function mutation in the sodium channel. This mutation prevents the degradation of the channel and leads to overactivity. The early and severe hypertension common in Liddle's syndrome is due to excessive sodium reabsorption, which causes systemic volume overload.

Primary hypertension, however, is unlikely to be due to a single gene mutation. There have been many genes associated with an increased risk of hypertension, but the individual contributions of each gene are currently unknown. Based on animal models, there is evidence that genes active in the kidney are the largest contributors to genetic-based hypertension. There is evidence that the AT, adducin, and connexin 40 genes have a pathogenetic role in high BP.

Stress and primary hypertension

Stress is believed to contribute to the development of hypertension. Physiological stress leads to activation of the SNS and can lead to vasoconstriction and changes to SVR. Stress associated with being seen in medical clinics (white-coat hypertension) is one of the leading causes of pseudoresistant hypertension. Over time, stress can lead to long-term hypertension; patients with repeated physiological stress have a higher incidence of elevated BP.

One way to combat stress is to increase physical activity. Lack of physical activity can contribute to essential hypertension by leading to higher stress levels, greater risk of obesity, and reduced cardiovascular function. Several epidemiological studies have demonstrated a link between low physical activity and higher BP, mainly through the contribution of increased body mass in less active persons.

Table 3.3. Genetics and certain rare types of secondary hypertension.

Disorder	Mode of inheritance	Genes	Mutation and functional consequences
Glucocorticoid-responsive aldosteronism	Autosomal dominant	*CYP11b1* and *CYP11b2*	Ectopic expression of aldosterone synthase activity in adrenal fasciculata
Apparent mineralocorticoid excess	Autosomal recessive	*11bHSD*	Loss-of-function mutation resulting in excess stimulation of the mineralocorticoid receptor; hypertension mediated by increased renal cortical collecting tubule ENaC activity
Mutations in mineralocortocoid receptor	Autosomal dominant	*NR3C2*	S810L missense mutation in the ligand-binding domain converts receptor antagonists (such as progesterone) to agonists; pregnancy exacerbates hypertension
Liddle's syndrome	Autosomal dominant	*SCNN1B*	*De-novo* missense mutation of the β-subunit of the EnaC
		SCNN1G	Mutation in the γ-subunit of the EnaC that deletes the cytoplasmic C terminus, resulting in excess sodium retention
Pseudohypo-aldosteronism type II	Autosomal dominant	*WNK1* and *WNK4*	WNK serine-threonine kinase defects resulting in hyperkalemia and hypertension
Mutations in peroximase proliferator-activated receptor-γ	Autosomal dominant	*PPARG*	Loss-of-function mutation resulting in insulin resistance, diabetes mellitus, and hypertension
Syndrome of hypertension, hypercholesterolemia, and hypomagnesemia	Mitochondrial inheritance	Not yet indentified	Maternal inheritance of a homoplasmic mutation causes a cytidine substitution in the mitochondrial tRNA

EnaC, epithelial sodium channel; *CYP11b1*, cytochrome P450, subfamily 11B, polypeptide 1; *CYP11b2*, cytochrome P450, subfamily 11B, polypeptide 2; *11bHSD*, hydroxysteroid 11-β dehydrogenase; *NR3C2*, mineralocorticoid (aldersterone receptor); *SCNN1B*, sodium channel non-voltage-gated 1β (epithelial); *SCNN1G*, sodium channel non-voltage-gated 1γ; *WNK1*, protein kinase; *WNK4*, protein kinase, lysine deficient; *PPARG*, peroxisome proliferator activated receptor-γ. (Adapted from Cowley AW (2006) The genetic dissection of essential hypertension. *Nat Rev Genet* **7:**829–840.)

Secondary hypertension

Clinicians must also assess possible secondary causes that may cause hypertension. Recognition of secondary hypertension is important because hypertension can often be markedly improved by treatment of the underlying condition, which includes obstructive sleep apnea, renal artery stenosis, pheochromocytoma, and Cushing's disease (see *Table 3.4* for a partial list). When a secondary cause is detected, it can be treated directly, often leading to improvement in BP. These conditions, discussed below, may require referral to a specialist for definitive diagnosis and treatment.

Renal disease

Hypertension itself can reduce renal function and is a major cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD). Patients with acute kidney injury (AKI) and CKD may become hypertensive due to renal dysfunction. The close association between renal function and BP is not surprising, as the kidney is responsible for fluid filtration and salt regulation, both of which directly impact circulating fluid volume. Long-term decreases in kidney function (e.g. in CKD) can lead to elevated BP. Studies have shown that the prevalence of hypertension is inversely correlated with the glomerular filtration rate (GFR). In one study, the hypertension prevalence rate increased from 65% to 95% of patients as the GFR decreased from 60 to 15 ml/minute/1.73 m^2.

Primary aldosteronism

Aldosterone functions by binding to mineralocorticoid receptors in the kidney, thereby increasing sodium reabsorption. Elevated production of aldosterone can deregulate the balance and lead to large increases in sodium and water retention. Patients with primary aldosteronism (PA) also have elevated BP due to changes in fluid handling. One method of treatment is to add a mineralocorticoid receptor antagonist to an existing antihypertensive treatment regimen. Spironolactone,

Table 3.4. Examples of secondary hypertension.

- Renal diseases:
  - Renal artery stenosis
  - Chronic kidney disease
  - Acute kidney injury
- Primary aldosteronism
- Pheochromocytoma
- Obstructive sleep apnea
- Cushing's syndrome
- Thyroid disease
- Hyperparathyroidism
- Brainstem compression
- Medications
- Pregnancy

used as a renal competitive aldosterone antagonist, has been shown on average to lower systolic BP by 25 mm Hg and diastolic BP by 12 mm Hg. Interestingly, other clinical trials have shown a decrease in BP using aldosterone antagonists even when PA is not suspected. This result suggests that spironolactone may be useful for patients with essential hypertension even when PA is not present.

Pheochromocytoma

Pheochromocytomas are tumors that secrete very large amounts of catecholamines, the same neurotransmitters that reflect SNS activity. The abundance the catecholamines leads to changes in SVR and CO and an increase in BP. The tumors are usually found in the adrenal medulla, but can occur in other locations within the sympathetic chain. Pheochromocytoma is a relatively rare cause of secondary hypertension, with fewer than 1% of all cases of secondary hypertension caused by these tumors. Approximately 85–95% of patients with a pheochromocytoma have hypertension, which may be either sustained or paroxysmal.

Sleep apnea

Obstructive sleep apnea represents repeated periods of reduced airflow during sleep because of an obstruction. Patients with obstructive sleep apnea experience multiple episodes per night, in some instances as many as five or more airway obstructions per hour. The obstruction in airflow results in asphyxia, and the lack of oxygen leads to hypoxia, which is the most likely for BP increases. Heart rate and stroke volume both change in response to hypoxia, which leads to changes in CO. Sleep apnoea can cause very large increases in short-term BP levels; systolic pressures immediately following an episode may be as high as 300 mmHg. One of the most efficacious treatments for obstructive sleep apnoea is continuous positive airway pressure breathing.

Other causes of secondary hypertension

Cushing's disease is caused by overproduction of cortisol. At high concentrations, cortisol can exhibit strong mineralocorticoid signaling that leads to hypertension. Interestingly, the morbidity and mortality associated with Cushing's disease is most often due to diastolic hypertension. Other types of endocrine deregulation, such as disorders of the thyroid, hyperparathyroidism, and acromegaly, are also associated with hypertension. There are numerous other disorders of signaling or hormone production that are associated with elevated BP.

Many drugs (prescribed and over-the-counter) may contribute to hypertension. Females may become hypertensive when taking oral contraceptives. Changing to other formulations of medication or other methods of birth control may improve BP control.

Finally, excessive alcohol intake may lead to hypertension, with people consuming two or more alcoholic drinks per day having a two-fold risk of developing hypertension. Decreased alcoholic intake can lead to BP reduction.

CHAPTER 4

NON-PHARMACOLOGICAL TREATMENT OF HYPERTENSION

Overview

High BP contributes to increased morbidity and mortality, especially due to CVD. Fortunately, much of this increasd risk can be reduced by restoring BP to normal levels. Patients with mild primary hypertension or prehypertension may not necessarily require medication to become normotensive, as lifestyle modifications may suffice to achieve BP treatment goals.

Lifestyle modification as a treatment for hypertension has many advantages over drugs, including a reduced cost burden. In addition, patients do not have to contend with the side-effects associated with antihypertensive medications, such as the coughing some patients develop when taking ACE inhibitors or even more serious effects such as heart failure, which can be precipitated by beta-blockers in some patients with underlying lft ventricular myocardial dysunction.

Lifestyle modification to control hypertension

Lifestyle modifications beneficial for hypertension control are in many cases also beneficial for attaining a general healthy lifestyle (*Table 4.1*). For example, changing diet and exercise regimens to treat hypertension have the added benefit of lowering risk factors for CVD and diabetes mellitus. Many of these lifestyle changes target factors that are thought to contribute to the pathogenesis of primary hypertension (e.g. tobacco use, alcohol intake, and excess sodium ingestion).

Table 4.1. Examples of lifestyle modification for controlling hypertension.

- Improvements in diet:
  - Increase fiber
  - Increase potassium, calcium, and magnesium
  - Decrease sodium
- Decrease alcohol
- Decrease body mass
- Decrease smoking
- Increase physical activity

Increased exercise

Exercise provides many health benefits, including better cardiovascular fitness, reduced stress, and improved lipid profiles. A long-term exercise regimen also reduces the risk of hypertension, whereas a lack of regular exercise leads to an increased incidence of hypertension. Regular exercise can reduce BP by as much as 5–15 mmHg in patients with primary hypertension. An analysis of many studies involving exercise determined that the average systolic reduction in BP in response to exercise is 6 mmHg systolic and 3 mmHg diaastolic. Similar results in BP reduction are also seen in prehypertensive patients. The effect of exercise on BP is most evident in the young and middle-aged.

The type, duration, and frequency of exercise influence BP. For long-term BP control, both strength training and aerobic exercise are beneficial, with aerobic exercise the more effective. Aerobic exercise intensity is more important than frequency, as long as certain baseline frequency levels are met. For example, vigorous exercise for one hour, three times a week may improve BP more than moderate exercise for 30 minutes, six times a week. The mechanism of BP reduction with exercise has yet to be definitively elucidated, although reduction of circulating norepinephrine over time is believed to contribute to this effect by reducing SVR and CO. Exercise also improves general cardiovascular health and can reduce body mass, thus helping counter obesity. These improvements may be additive to the benefits of exercise alone.

Despite the benefits of exercise on hypertension, caution must be taken during the actual performance of exercise. BP will generally rise during exercise and during the immediate post-exercise period. Increased physical activity stimulates the SNS, leading to increased activation of the adrenergic receptors and increased SVR and CO. During strength training, BP can rise to levels as high as 300/125 mmHg, mostly due to skeletal muscle contraction, which causes increased SVR and resultant BP rise. Aerobic exercise also increases CO, leading to increases in systolic BP, but changes in diastolic BP are less evident. Aerobic exercise often results in vasodilation of working muscle groups in order to increase blood flow to those muscles. Diastolic BP may remain unchanged or even fall slightly because of decreased SVR associated with aerobic exercise.

Weight reduction

High-calorie diets and low rates of physical activity in many cultures have resulted in excess weight, with obesity prevalence increasing to near epidemic proportions. Therefore, weight reduction is an important aspect of lifestyle modification for treatment of hypertension in all overweight people. Several studies have demonstrated that reducing body weight leads to a reduction in BP as well as a decrease in the need for antihypertensive drugs. For example, reducing body weight by 10% leads to an average decrease in BP of 4.3/3.8 mmHg. A meta-analysis showed that for each one kilogram (2.2 lb) reduction in body weight, systolic BP decreases on average by 1.6 mmHg, while diastolic pressure decreases by 1.3 mmHg. Long-term studies also support the correlation of body weight and elevated BP. A study that followed patients over a two-year period demonstrated that for every 10 kg (22 lb) reduction in body weight, BP decreased by an average of 6/4.6 mmHg. An eight-year study of 1,200 overweight people demonstrated a 22% drop in the risk of

developing hypertension following an average weight loss of 6.8 kg. The reduction in risk was even higher for people aged 50–65 years, whose risk decreased 26% with weight reduction.

Excess body weight results in many changes that could contribute to hypertension. These include increased CO, alterations in the left ventricle, reduced function of the kidneys, and changes in insulin signaling. Reduction in excess weight can improve many of these conditions. Reducing CO will lead to less strain on the cardiovascular system, thus preventing continued LVH and remodeling of the vasculature. Lowering body weight can also contribute by improving endothelial cell function through increases in vasodilation by nitric oxide-based signaling. Insulin sensitivity and glucose tolerance are also improved by weight loss. Improved insulin responsiveness restores the vasodilation due to insulin in normotensive patients, thus improving regulation of SVR.

Changes in diet

Alterations in diet can be beneficial in lowering BP by decreasing obesity, reducing sodium intake, and improving deficiencies in other minerals. The Dietary Approach to Stop Hypertension (DASH) Study confirmed the benefits of a healthy diet in hypertension. This study compared the average diet with a diet with increased fruits and vegetables and also with a diet high in fruits and vegetables, low-fat dairy, and reduced saturated fat. People on the DASH diet showed the greatest reduction in BP, followed by the diet high in fruits and vegetables (Figures 4.1

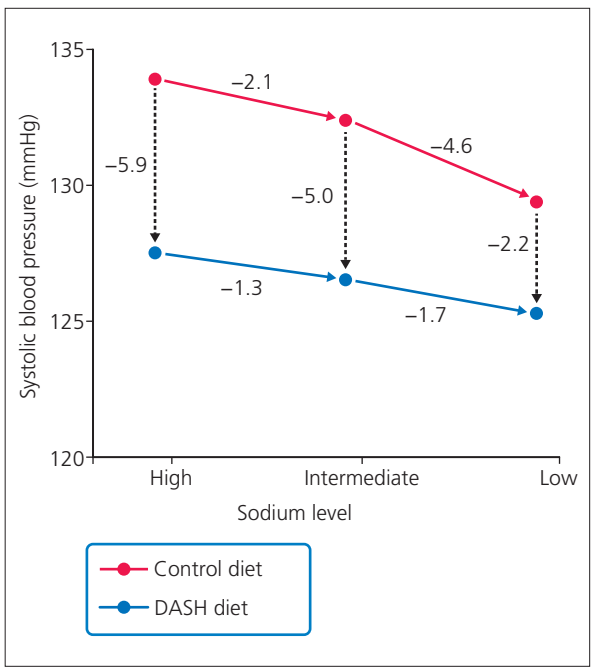


Fig. 4.1 Effect of dietary salt intake on blood pressure levels. (Adapted from Sacks FM, Svetkey LP, Vollmer WM *et al*. (2001) Effects on blood pressure of reduced dietary sodium and the dietary approaches to stop hypertension (DASH) diet. *N Eng J Med* **344:**3–10.)

and 4.2). The effect was most pronounced in patients classified as having hypertension, among whom there was an average BP decrease of 11.4/5.5 mmHg. When coupled with caloric reduction, sodium restriction (according to results of the DASH Study) adds to the effect of diet on BP reduction. Diet also has a modifying effect on the progression of hypertension. A five-year study of patients with prehypertension observed the effects of usual diets or diets with reduced sodium, reduced alcohol, and weight reducing food. Over the course of the study, almost 20% of patients on the usual diet developed hypertension compared with less than 10% of those on the restricted sodium diet.

Certain components of the diet have been shown to play particularly important roles in preventing hypertension. For example, sodium reduction and potassium and calcium increases lower BP. The effect due to increased calcium is minor (average 1.44/0.8 mmHg reduction), while increased potassium usually causes a greater decrease in BP. Various additives can also improve BP, such as diets that are high in fish oil, which decrease systolic BP by 6 mmHg and diastolic BP by 4 mmHg. The mechanism of reduction is unknown and the long-term health effects of a high fish oil diet are also unknown. Vegetarian diets reduce BP in part due to their high-fiber content.

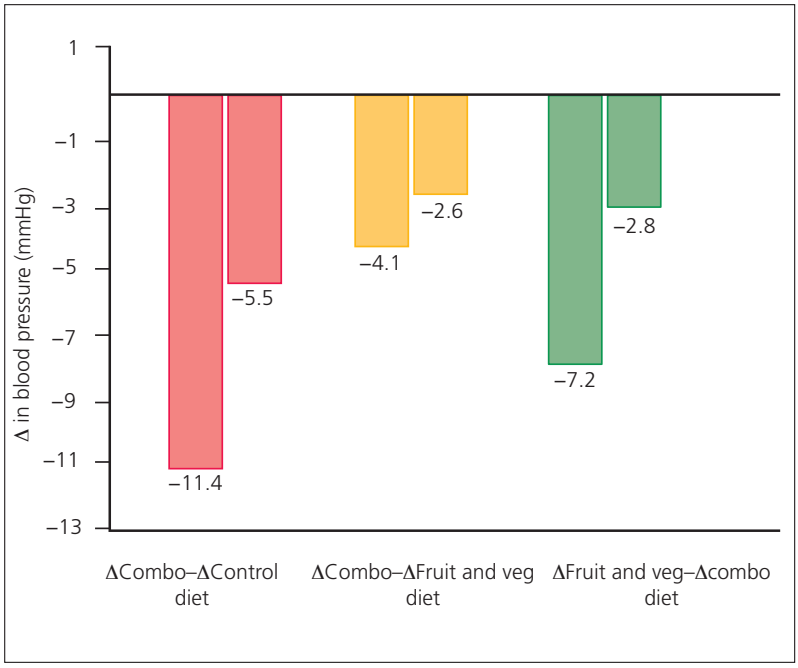


Fig. 4.2 Changes in blood pressure with the Dietary Approach to Stop Hypertension diet. (Adapted from Appel LJ, Moore TJ, Obarzanek E *et al*. (1997) A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N Eng J Med* **336:**1117–1124.)

Sodium reduction

Excess dietaary sodium intake is a risk factor for increased BP, and sodium reduction reduces BP in normotensive, prehypertensive, and hypertensive individuals. A meta-analysis demonstrated that reducing sodium intake to only 75 mEq/day causes a reduction in BP by four weeks after sodium restriction is begun. Normotensiv people had a reduction in BP of 2/1 mmHg and hypertensive patients had a reduction of 5/3 mmHg. The BP effects of sodium reduction can take several weeks to become evident, therefore long-term commitment to this dietary change is important for BP control.

Restriction of sodium intake improves BP by improving kidney function. Sodium retention becomes less a factor when sodium intake is restricted, resulting in reductions in fluid volume and CO. It is important that patients avoid severe reductions in sodium intake, however, as this can lead to undesirable effects such increased propensity to dehydration, especially during hot weather.

Reduced sodium intake increases the effectiveness of many antihypertensive (and other) drugs, because reduced volume retention increases drug fluid concentration. Sodium reduction also reduces volume overload and its effects, such as decreased peripheral edema in people with lower extremity venous insifficiency. Reduced fluid volume activates the RAAS, leading to an increase in plasma renin concentration, which makes BP levels more dependent on RAAS activity, and can lead to greater efficacy of drugs that target the RAAS pathway, especially ACE inhibitors and AT II receptor blockers (ARBs). The effectiveness of the antihypertensive class of calcium channel blockers (CCBs) is not increased by reduced sodium diet.

Despite what has been stated in the past regarding 'sodium reduction as a means to control BP, the 'salt debate' continues. Two meta-analyses claimed that salt reduction had very little or almost negligible effect on BP in normotensive individuals. These and other smaller trials cast doubt on an apparent 'link' between salt intake and BP, and they have also been used to oppose public health recommendations for population reductions in salt intake.

In a more recent population-based cohort study, it was shown that systolic BP, but not diastolic BP, changed over time and this change correlated with the change in sodium excretion. However, this association did not translate into a higher risk of hypertension or CVD complications. In this study, lower sodium excretion was associated with higher CVD mortality. Another recently published meta-analysis failed to show strong evidence of an effect of dietary sodium reduction on cardiovascular mortality and events.

Recognizing the controversy of the role of dietary sodium and cardiovascular risk, future research should focus on rigorous, large long-term randomized controlled trials capable of demonstrating 'definitively' the cardiovascular benefit of dietary salt reduction. Such trials need to assess population level interventions that are likely to lead to sustained reductions in salt intake and are commensurate with current public health guidelines. Ideally, the effects of voluntary salt reductions by food industries will also be assessed, as these may hold greater promise for more practical means of actually reducing salt intake in the population at large rather than focusing only on dietary advice for at-risk individuals.

Alcohol reduction

Reducing alcohol intake lowers BP in many individuals. Although many studies have shown that moderate daily alcohol intake, especially drinking red wine, has positive health benefits, overconsumption of alcohol raises the BP. Hypertension is twice as common in people who consume two alcoholic drinks per day (e.g. two 12 oz [355 ml] beers) compared with people who abstain completely from alcohol use. The effect of alcohol on hypertension incidence appears to be related to the amount of alcohol consumption. Reducing alcohol consumption is one of the quickest lifestyle modifications for improving BP levels. One meta-analysis found that the average reduction in BP is 3.3/2 mmHg with cessation of alcohol ingestion. This reduction is dependent on continued cessation of alcohol intake, as BP rises to prior levels if alcohol consumption resumes.

Other lifestyle modifications

There are several other lefestyle modifications that will lead to improvement in BP. Caffeine consumption is known to cause a short-term increase in BP, with regular caffeine intake raising BP by as much as 5/3 mmHg. For some patients, reducing caffeine intake may lead to reduction in BP. Another important lifestyle change is tobacco cessation, as nicotine can also lead to short-term increases in BP, partly due to increased vasoconstriction. Patients who stop smoking also derive numerous other health benefits, particularly risk for CVD (beyond the efects of lower BP) and cancer.

CHAPTER 5

MANAGEMENT OF HYPERTENSION

Overview

When a patient's BP does not meet target levels following a sufficient period of lifestyle modification, antihypertensive drug therapy is universally recommended as the next step. Although different guidelines propose differing initial therapies, they all agree that antihypertensive drug therapy is one of the major reasons for the decline in stroke and coronary heart disease mortality over the last 50 years. Compared with placebo or no treatment, active drug treatment in clinical trials significantly reduced fatal or non-fatal stroke by ~33%, myocardial infarction by ~15%, heart failure by ~36%, and all-cause mortality by ~12%. Most recent meta-analyses suggest that the cardiovascular protective effects of all antihypertensive drugs can be most easily attributed to their BP-lowering properties, despite evidence that they do so by different molecular mechanisms.

Antihypertensive therapy

The goals of blood pressure treatment

Although epidemiological data indicate that BP less than 115/75 mmHg is associated with the lowest risk of cardiovascular morbidity and mortality, several recent studies have concluded that excessive lowering of BP is not necessarily better for preventing cardiovascular events. Traditionally, the BP target has been less than 140/90 mmHg for all hypertensive patients. Recently, a lower target of less than 130/80 mmHg has been recommended for patients with diabetes mellitus, CKD, or established heart disease. However, these targets are controversial because the evidence base consists of subgroup analyses of clinical trials and/or extrapolations from other therapeutic areas (e.g. lipid-lowering therapy, for which a progressively lower target is beneficial for higher-risk patients). Relatively few outcome-based clinical trials have been carried out that randomized hypertensive subjects to different BP targets. A recent exception is the Action to Control Cardiovascular Risk in Diabetes – Blood Pressure (ACCORD–BP) Trial, which showed no significant benefit in hypertensive diabetics randomized to a systolic BP target of less than 120 mmHg. Because of the lack of direct clinical trial evidence, various guidelines offer different BP targets for different hypertensive subgroups, although most agree that higher-risk subjects ought to be treated to a lower than usually recommended BP, despite the lack of supporting evidence.

Monotherapy

There is a growing awareness that a small minority of hypertensive patients can reach BP targets using only a single antihypertensive drug. However, guidelines that offer different recommendations for initial therapy of hypertension tend to converge once the initial drug's effect on BP is found to be insufficient. The most widely used classes of of drugs for initial antihypertensive therapy include (in historical order): diuretics, calcium antagonists, ACE inhibitors, and ARBs. Some experts would add beta-blockers to this list, but recent meta-analyses (based in large part on clinical trials that used atenolol) suggest that initial use of a beta-blocker is significantly inferior to other antihypertensive drugs in preventing cardiovascular events in hypertensive patients.

Most guidelines agree that if a patient has a condition for which a specific type of antihypertensive drug improves the prognosis, that medication can be used as initial therapy to lower BP. For example, a hypertensive survivor of a recent myocardial infarction (MI) would benefit from a beta-blocker that is recommended to reduce the risk of death or recurrent infarction. All guideline committees recognize the existence and importance of contraindications (including allergies), even for drugs that might otherwise be first-line choices. For uncomplicated hypertensive patients, different guidelines disagree about the most appropriate initial therapy. In the USA, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) influenced the authors of JNC7 to recommend a low dose of a thiazide or thiazide-like diuretic for 'most' uncomplicated stage 1 (BP 140–159/90–99 mmHg) patients with hypertension. In the UK, the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) favored the calcium antagonist, ith or without an ACE-inhibitor, rather than a beta-blocker with or without a diuretic. Therefore, UK guidelines recommend a CCB or diuretic for older people or blacks with hypertension, and an ACE inhibitor for younger, white people. The European guidelines recognize that few patients will attain individual BP targets with monotherapy, and they therefore devote more emphasis on appropriate antihypertensive combinations rather than initial treatment recommendations.

Combination therapy

Recent meta-analyses suggest that for most antihypertensive drug classes, combining two different classes of drugs at moderate doses is more likely to lower BP than prescribing the dose of any one drug to its maximum level. This approach has an advantage in helping avoid common adverse drug effects. The combination of a low-dose diuretic and either an ACE inhibitor, an ARB, or a (direct) renin inhibitor (DRI) is likely to maintain eukalemia and, perhaps, euglycemia. Combining a CCB with an ACE inhibitor, or (probably) an ARB, tends to reduce the incidence and severity of pedal edema that occurs with higher-dose CCBs. Many single-pill combinations are available that contain such agents; this has the potential to improve long-term adherence to antihypertensive drug therapy, which is necessary for optimal cardiovascular risk reduction. Although JNC7 recommends that combination therapy should usually include a diuretic, the results of the recent Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) Trial are likely to broaden the choices – beyond diuretics – for combination therapy in the next set of USA guidelines. The USA Food and Drug Administration has recently

approved several single-pill combination products for first-line therapy, typically when the probability of achieving the target BP with a single agent is small.

An algorithmic approach to the choice of antihypertensive drug treatment is presented in the NICE Guidelines 2011. Commonly used antihypertensive drugs and their dosages are listed in *Table 5.1*.

Table 5.1. Antihypertensive drugs and their oral dosages.

	Dose (mg)/day		Dose (mg)/day
Diuretics		**β-blockers**	
Hydrochlorothiazide	12.5–50	Propranolol	40–240
Indapamide	1.25–5	Atenolol	25–100
Chlorthalidone	12.5–50	Metoprolol	50–200
Metolazone	2.5–10	Bisoprolol	2.5–20
Furosemide	20–240	Nebivolol	5–40
Bumetanide	0.5–4	Pindolol	10–50
Torsemide	0.5–4		
Ethacrynic acid	25–100		
Potassium sparing drugs		**α+β blockers**	
Amiloride	5–10	Labetalol	200–1000
Triamterene	25–100	Carvedilol	12.5–100
Aldosterone antagonists		**α1-blockers**	
Spironolactone	25–100	Prazosin	2–20
Epleronone	50–100	Doxazosin	1–16
		Terazosin	1–20
ACE inhibitors	5–40	**Central α-agonists**	
Benazepril	25–150	Clonidine	0.2–1.0
Captopril	5–40	Methyldopa	500–2,500
Enalapril	5–40	Moxonidine	0.2–0.6
Lisinopril			
Perindopril	4–16	**Peripheral sympathetic blockers**	
Trandolapril	1–4	Reserpine	0.05–0.25
		Guanethidine	10–100
Calcium channel blockers		**Angiotensin receptor blockers**	
Amlodipine	2.5–10	Telmisartan	40–80
Felodipine	2.5–20	Valsartan	80–320
Nifedipine	30–120	Losartan	50–100
Nicardipine	60–120	Candesartan	8–32
Cilnidipine	5–20	Eprosartan	400–800
Verapamil	90–480	Irbesartan	150–300
Diltiazem	120–480	Olmesartan	20–40
Direct arterial dilators		**Direct renin inhibitor**	
Hydralazine	50–200	Aliskerin	150–300
Minoxidil	5–100		

Key points about antihypertensive drugs

Diuretics

Expansion of fluid volume and extracellular fluid is an important etiological factor in the pathogenesis of primary hypertension. From the inception of drug therapy for hypertension, diuretics have remained the cornerstone of management either as monotherapy or as an integral part of combination therapy. Until now, diuretics have been recommended as the initial drug of choice for hypertension by all national and international guidelines. Thus, diuretics are pivotal to the long-term treatment of hypertension. Thiazide diuretics have been used most often in clinical trials, outcome studies, and clinical practice, and are effective when renal function is normal. In patients with CKD or educed GFR, loop diuretics are preferred to thiazides.

The effects of thiazide diuretics on BP are grouped into acute, subacute, and chronic phases. It is during the chronic phase that thiazides are most useful in treating hypertension. The main site of diuretic action is the sodium/chloride pump in the renal distal convoluted tubule (Figure 5.1). Although thiazides cause sodium/water excretion during the acute and subacute phases, the long-term hemodynamic effects are mediated by reducted SVR. Thiazide diuretics can be taken once per day. In the elderly, the starting dose of thiazide is 12.5 mg daily, titrated gradually, and only rarely neeeded in doses higher than 50 mg daily.

Certain patient groups exhibit greater sensitivity (and BP response rates) to thiazide diuretics (e.g. elderly, blacks, diabetics). In general, patients with volume expansion (low plasma renin activity) show a good response to diuretics. A low-sodium diet enhances the efficiency of diuretics. Diuretics are generally safe for long-term treatment of hypertension, but patients should be monitored for side-effects, especially volume depletion, hyponatremia, hypokalemia, hyperuricemia, hyperglycemia, and lipid abnormalities. Magnesium loss may accentuate diuretic-induced hypokalemia.

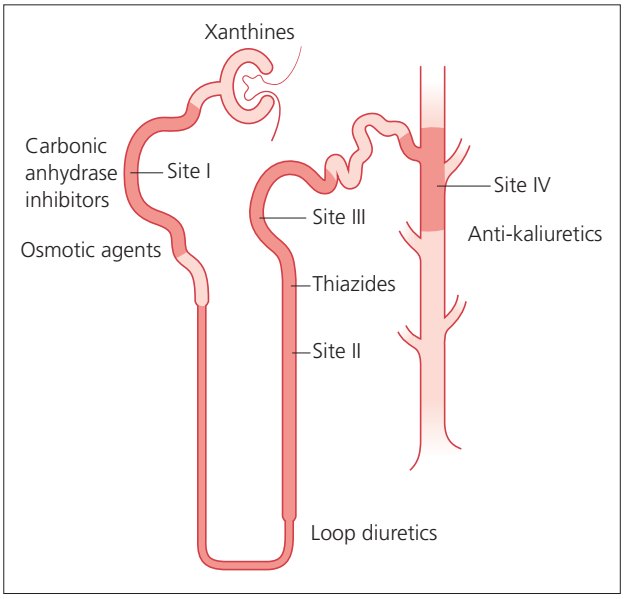


Fig. 5.1 Sites of action of diuretics.

Loop diuretics are generally not indicated in patients with normal renal function, except in the presence of edematous conditions. They are indicated (and are often necessary) when there is reduced renal function. Loop diuretics are stronger than thiazides but have shorter durations of action; therefore, they should be given at least twice daily. Loop diuretics act on the thick ascending loop of Henle to block sodium and chloride reabsorption. There are no long-term or outcome studies with loop diuretics in hypertension, whereas for thiazide diuretics there are several positive outcome studies such as the Veterans Administration (VA) Cooperative Study, the ALLHAT, the Multiple Risk Factors Intervention Trial (MRFIT), and the Systolic Hypertension in the Elderly Program (SHEP).

Diuretics were the first drug class to show outcome benefits in hypertensive patients, although even in early trials they were usually used in combination with other agents. They primarily act by reducing extracellular sodium and fluid volume, although some diuretics also possess vasodilatory properties, perhaps at the calcium channel site. Thiazide and thiazide-like diuretics, which act primarily in the renal distal convoluted tubule, are the most widely used agents if this class, particularly in patients with normal renal function, although the doses in current use are much lower than those used in early clinical trials. The lower doses reduce the incidence and severity of adverse effects, particularly hypokalemia, which may cause some of the long-term adverse metabolic effects of thiazides. The BP-lowering effects of diuretics can be compromised by dietary or other sources of sodium, and by non-steroidal anti-inflammatory drugs (NSAIDs). Most authorities agree that chlorthalidone is more potent in lowering BP, and has a longer duration of action, than hydrochlorothiazide (HCTZ); these properties may account for the seemingly disparate results of the ALLHAT (in which chlorthalidone was 'superior in preventing one or more major forms of cardiovascular disease'), compared with the ACCOMPLISH Trial (in which benazepril plus HCTZ was inferior to benazepril plus amlodipine).

Diuretics that act primarily in the thick ascending limb of the loop of Henle (so-called 'loop diuretics') are usually required for patients with stage 3 and more severe forms of CKD. They are also often used for patients with heart failure, but are typically given twice daily. If short-acting furosemide or bumetanide is given once daily, fluid accumulation can occur during the 12–18 hours before the morning dose, particularly if the evening meal contains most of the daily dietary sodium. Both loop and thiazide diuretics are sulfonamides, so they are usually contraindicated for patients with true sulfa allergies; in such patients, oral ethacrynic acid is available for twice-daily use.

Aldosterone antagonists have been in clinical use for many years. Because of the recent understanding of aldosterone as a mediator of CVD and hypertension, there is renewed interest in the clinical efficacy of aldosterone antagonists in treating hypertension and CHF. In addition to the original blocker of aldosterone (spironolactone), a selective aldosterone antagonist, epleronone, is also currently available. Aldosterone exerts manifold physiological and pathophysiological effects that cause an expansion of extracellular fluid volume, cardiovascular hypertrophy, vasoconstriction, and elevation of systemic BP. Therefore, aldosterone antagonists are used as a part of the combination therapy for resistant hypertension and CHF. Aldosterone antagonists have long been the drugs of choice for medical management of primary aldosteronism (PA).

Aldosterone antagonists are best used in combination with thiazide diuretics. In addition to beneficial cardiovascular effects, aldosterone antagonists, by their actions on the kidney, cause positive potassium balance and induce modest natriuresis. In experimental studies, they reverse cardiac fibrosis. Aldosterone antagonists (in particular, spironolactone) are extremely useful in the treatment of hypertension, as several studies have shown remarkable efficacy of spironolactone in the treatment of resistant hypertension. The selective antagonist of aldosterone, eplerenone, is as effective as spironolactone. Aldosterone antagonists can cause side-effects such as abdominal discomfort, gynecomastia, and sexual disturbances, but epleronone is less likely to cause these side-effects. Potassium retention and hyperkalemia can occur with aldosterone antagonists in susceptible individuals, such as patients with renal impairment and patients taking other drugs that block the RAAS (Figure 5.2). Therefore, particular caution is advised when using aldosterone antagonits in patients prone to developing hyperkalemia.

Potassium-sparing diuretics are most often used in combination with thiazides. The two aldosterone inhibitors (spironolactone and eplerenone) are used largely in patients with heart failure and patients with hyperaldosteronism.

Calcium channel blockers

CCBs were originally intended for treating patients with coronary artery disease, but were subsequently approved for the treatment of hypertension. By the nature of their action, CCBs block the L-type voltage channel and thus cause vasodilation. Dihydropyridine (DHP) CCBs (e.g. nifedipine, amlodipine, nicardipine) are more potent as antihypertensive agents than non-DHP CCBs, such as verapamil and diltiazem. The application of DHP CCBs is wider in hypertension, whereas diltiazem and verapamil are preferentially used for coronary artery disease and cardiac arrhythmias. Since DHP CCBs cause profound vasodilation, sympathetic activation may occur, but this is not seen with less potent non-DHP CCBs. DHP CCBs may cause flushing, headache, and peripheral edema. Non-DHP CCBs may cause constipation and bradycardia. Gingival hyperplasia is a side-effect

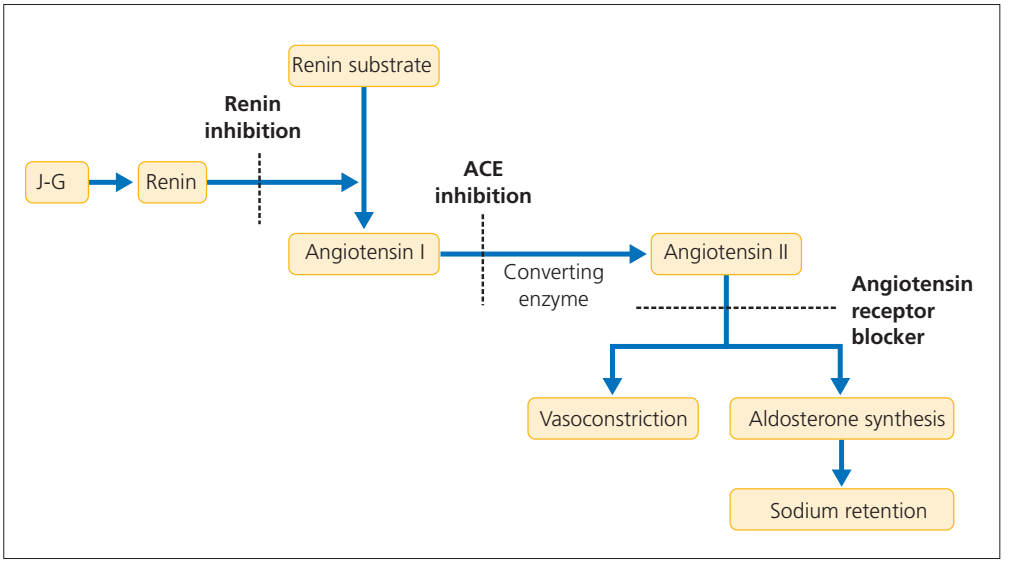


Fig. 5.2 The renin–angiotensin–aldosterone system.

of DHP CCBs. Amlodipine-based therapy showed a benefit over atenolol-based therapy in the ASCOT Trial and over valsartan based-therapy in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) Study. Verapamil-based therapy was more beneficial than atenolol-based therapy in the International Verapamil SR-Trandolapril (INVEST) Study.

The CCBs can be divided into two pharmacological subgroups: DHPs and verapamil/diltiazem (and related compounds). The latter typically have negative inotropic and chronotropic properties, whereas the DHPs are more vasoselective and can increase heart rate, especially acutely when taking immediate-release preparations. All CCBs inhibit flux of calcium into smooth muscle cells, causing vasodilation. Many CCBs are approved for patients with angina pectoris. Verapamil can cause dose-related constipation and immediate-release DHP compounds can cause flushing, tachycardia, and dose-dependent pedal edema; only the latter is seen with long-acting preparations. The BP-lowering effect of CCBs is generally little affected by dietary sodium or NSAIDs. Although past studies suggested that CCBs were associated with a significantly higher risk of cardiovascular events than other antihypertensive drug classes, recent meta-analyses of comparative clinical trials indicate that they are as effective in preventing both stroke and coronary events as diuretics. However, the risk of heart failure is significantly increased (by about 44%), regardless of the CCB type used. This may be related, in part, to the propensity (especially for DHP compounds) to cause dose-dependent fluid retention, and for verapamil and diltiazem to reduce left ventricular ejection fraction.

Inhibitors of the renin–angiotensin–aldosterone system

The pathophysiological importance of AT II in hypertension and in causing TOD derives from its adverse effects on blood vessels and tissue blood flow. In addition to its hemodynamic effects, AT II exerts a number of pleotropic effects, including some involving coagulation pathways. Therefore, blockade of the RAAS with ACE inhibitors or ARBs has significant therapeutic implications. Inhibition of the RAAS with ACE inhibitors or ARBs not only reduces the BP in patients with hypertension, it also protects against TOD. A variety of ACE inhibitors and ARBs are available for the treatment of hypertension, CHF, diabetic nephropathy (DN), and other 'high-risk' patients.

Although ACE inhibitors and ARBs can be differentiated on the basis of their pharmacological, pharmacokinetic, and metabolic effects, these additional properties generally do not aid the clinician in the selection of drugs for the treatment of hypertension. While it has been proposed that highly lipophilic ACE inhibitors, such as ramipril and quinapril, offer 'tissue selectivity', this attribute provides no clinical superiority. The predominant mechanism of action of ACE inhibitors and ARBs is on RAAS blockade (Figure 5.3), with an ancillary mechanism in inhibition of the SNS. To what extent bradykinin activation contributes to the hemodynamic effects of ACE inhibitors is uncertain. ARBs lower the BP to the same extent as ACE inhibitors, but without a discernible effect on bradykinin potentiation. Although ACE inhibitors and ARBs are more effective in patients with high plasma renin activity (PRA), treatment guidelines do not recommend measurement of PRA as a guide to drug selection. Since a majority of patients with hypertension require a combination of antihypertensive drugs with different mechanism(s) of action, the level of PRA is not crucial for selecting an ACE

inhibitor or an ARB. ACE inhibitors should be combined with other classes of antihypertensive drugs for optimal efficacy. The combination of an ACE inhibitor plus a diuretic or a CCB is particularly efficacious in treating hypertension. Patients taking ACE inhibitors should be monitored for adverse effects (e.g. cough, angioedema, azotemia, hyperkalemia).

ARBs have similar efficacy as ACE inhibitors for treating hypertension by blocking the actions of AT at the AT receptor. ARBs may differ pharmacologically (e.g. pro-drug conversion, metabolism, half-life, bioavailability), but their clinical efficacy and tolerability are similar to ACEs. By inhibiting the actions of the RAAS at the receptor, ARBs may cause a reactive increase in PRA, but this has no negative effect because the actions of AT are inhibited at the blood vessel site. ARBs are indicated (like ACE inhibitors) for hypertension, DN, CHF, and 'high-risk' patients. The adverse biochemical/renal side-effects of ARBs are similar to those of ACE inhibitors, but cough and angioneurotic edema are unlikely to occur with ARBs. All RAAS blockers are contraindicated in pregnancy. ARBs are most effective when used in conjunction with diuretics and other antihyperensive drugs such as CCBs.

Angiotensin-converting enzyme inhibitors

ACE inhibitors inhibit the conversion of AT I to AT II, producing vasodilation and reduced BP. Because hydrolysis of bradykinin is also inhibited by these drugs, cough (7–12% of patients) and angioedema (0.7%) can occur. As with any drug that inhibits the RAAS, ACE inhibitors can cause AKI in patients with renal artery stenosis. They are also teratogenic and cause birth defects, therefore are contraindicated in pregnancy.

ACE inhibitors are usually effective in lowering BP, but their efficacy is reduced by dietary or other sources of sodium, and renal function may be compromised if they are taken along with NSAIDs. In clinical trials, they are among the most effective drugs in preventing coronary heart disease, which some authorities believe is 'a benefit beyond BP control'. ACE inhibitors are also eficacious for patients with heart failure or CKD (particularly type 1 diabetics and non-diabetic CKD). All ACE

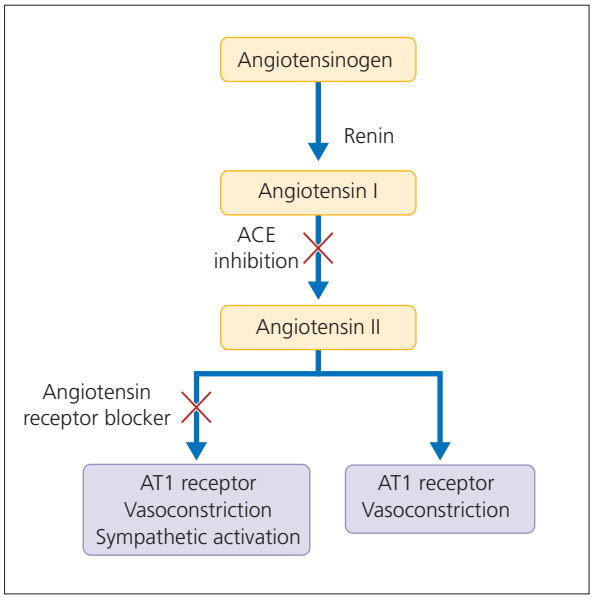


Fig. 5.3 Pharmacological blockade of the renin–angiotensin–aldosterone system.

inhibitors are available in generic form, so they are often favored by formulary committees over other inhibitors of the RAAS for financial reasons.

Angiotensin receptor blockers

ARBs inhibit binding of AT II to its subtype 1 receptor, which also results in vasodilation and lowering of BP. ARBs do not cause as much cough or angioedema as ACE inhibitors, although the risks of teratogenicity or AKI in patients with renal artery stenosis are similar. Some ARBs have been approved for type-2 DN and heart failure, either alone or in combination with ACE inhibitors. Several recent clinical trials of ARBs have provided disappointing results when compared with either CCBs (VALUE) or placebo (Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease [TRANSCEND], Prevention Regimen for Effectively Avoiding Second Strokes [PRoFESS] Study). However, the design of these trials has been criticized, because either the treatment drug doses were too low to cause equivalent BP lowering (e.g. VALUE) or the randomized agents were given in addition to other antihypertensives and other preventive therapies, rather than as initial treatments (TRANSCEND, PRoFESS). There are no direct comparisons of diuretics with ARBs, as nearly all ARB trials used a diuretic as second-line therapy. The major advantage of ARBs seems to be their relatively benign adverse effects profile, which probably accounts for their having the highest persistence rates of all antihypertensive drugs used in general clinical practice. The combination of an ARB plus an ACE inhibitor was found (1) to lower BP a little more than using either drug alone; (2) insignificantly improve clinical outcomes; and (3) be associated with a much higher rate of adverse effects (especially renal) in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET). This trial has shown that telmisartan, an ARB, is as effective as ACE inhibitors in preventing cardiovascular complications.

Direct renin inhibitors

In recent few years, compounds that inhibit the binding of renin to angiotensinogen and block the production of AT I have been developed. These compounds block the RAAS at its rate-limiting step and lower BP in a slightly dose-dependent fashion. The first compound of this class to market has an excellent tolerability profile and combines well with a low-dose diuretic, a CCB, and an ARB, although hyperkalemia and impaired renal function have occurred with the ARB combination. Because renin inhibitors are a new class of drugs, no long-term outcomes studies are available, but the compound has shown benefit in short-term trials using surrogate outcomes in patients with heart failure, albuminuria, and LVH.

Recently, an Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints (ALTITUDE, an international, randomized, double-blind, placebo-controlled, parallel-group study) was designed to determine whether dual RAAS blockade with the DRI aliskiren in combination with an ACE inhibitor or an ARB would reduce major (cardiovascular and renal) morbidity and mortality in a broad range of high-risk patients with type-2 diabetes mellitus. However, this study was terminated prematurely because an increased incidence of adverse events (e.g. non-fatal stroke, renal complications, hyperkalemia, hypotension after 18–24 months) was demonstrated in patients taking aliskiren combined with an ACE inhibitor or an ARB.

Beta-blockers

Beta-adrenergic blocking drugs have been popular antihypertensive drugs for many years. However, recent meta-analyses strongly suggest that beta-blockers lack cardioprotective effects in patients with hypertension. Although these data included studies using older beta-blocker drugs such as atenolol, the role of beta-blockers for treating hypertension has been questioned. Newer vasodilating beta-blockers, such as nebivolol and carvedilol, are as effective as older beta-blockers in treating hypertension and they also have advantageous metabolic effects and a better side-effect profile. Beta-blockers exert their antihypertensive effects by not only inhibiting the SNS, but also by blocking the renin release mechanism. All beta-blockers, irrespective of their pharmacological properties (cardioselectivity, lipid solubility, and intrinsic sympathomimetic activity), have similar BP lowering effects. There are several reasons why older beta-blockers may not be beneficial, including short duration of action, unopposed alpha-mediated vasoconstriction, and lack of an effect on aortic (central) BP. In contrast, the vasodilating beta-blockers have a longer duration of action, cause vasodilation, lower the aortic (central) BP, and do not cause classic beta-blocker side-effects such as fatigue, cognitive difficulty, weakness, erectile dysfunction, and bronchosposm.

Beta-blockers are beneficial in patients with coronary artery disease and compensated CHF and this has been proven by several clinical trials. Direct vasodilating beta-blockers have a number of hemodynamic and metabolic advantages over traditional beta-blockers, but there is a paucity of outcome data in patients with hypertension.

Although traditionally an acceptable first-line therapy for hypertension, beta-blockers (particularly atenolol, which comprises over 70% of clinical trial data) are not currently recommended by either USA or UK guidelines as initial therapy for uncomplicated hypertensive patients. Four possible mechanisms have been invoked for the antihypertensive effect of beta-blockers: (1) inhibition of renin release from the juxtaglomerular apparatus of the kidney; (2) reduction of tonic sympathetic outflow from the central nervous system; (3) reduction of myocardial contractility; and (4) arterial vasodilation. Other mechanisms include effects on water solubility, intrinsic sympathomimetic activity, membrane-stabilizing activity, and other (e.g. alpha$_1$-blocking activity, enhancement of nitric oxide bioavailability). Several beta-blockers are effective as second-line therapy (after ACE inhibitors) for heart failure. Adverse effects include bradycardia, fatigue, bronchoconstriction, dyspnea on exertion, and impairment of recognition of hypoglycemia in brittle diabetics. Many beta-blockers decrease high-density lipoprotein cholesterol levels, raise triglycerides, and may impair glucose tolerance. They are, nonetheless, very useful for reducing pulse rate and BP, and are often used in patients with aortic dissection and other indications.

Alpha-blockers

Selective alpha$_1$-receptor blocking drugs, such as prazosin and doxazosin, lower BP by reducing SVR. The antihypertensive efficacy of alpha$_1$-receptor blocking drugs equals that of beta-blockers and diuretics. Despite their attractive mechanism of action, alpha$_1$-receptor blocker use has declined because of a lack of favorable outcome studies. For example, ALLHAT results showed that the alpha$_1$-blocker doxazosin increased the risk of CHF. The main use of alpha$_1$-receptor blockers at the present time is in the management (in combination with other drugs) of benign

prostatic hypertrophy. Guidelines have downgraded the place of alpha$_1$-blockers in the treatment for hypertension. It is paradoxical that alpha$_1$-blockers do not improve outcomes in view of their favorable effects on LVH, glucose homeostasis, and lipid metabolism.

Alpha-blocking drugs block neuromuscular transmission by occupying the post-synaptic alpha$_1$ adrenoceptor on the smooth muscle cell, causing vasodilation. Their major adverse effects are dizziness, headache, and orthostatic hypotension (particularly 'first-dose' hypotension) and an increased risk of falls and hip fractures. Since the early termination of the doxazosin arm of the ALLHAT because of the significantly increased risk of combined cardiovascular events (especially heart failure), alpha-blockers have been relegated to second-line therapy for uncomplicated hypertension; doxazosin was used successfully as the third-line therapy in the ASCOT.

Other antihypertensive drugs

Clonidine and other centrally-acting alpha$_2$-agonists (e.g. methyldopa, guanfacine) lower BP by decreasing sympathetic outflow from the central nervous system; in small doses this causes vasodilation and lowering of BP. In larger doses, sedation, dry mouth, drowsiness, and other symptomatic adverse effects occur, which presumably explain why clonidine was the least tolerated drug in the Department of Veterans Affairs Monotherapy Trial. Sudden discontinuation of short-acting alpha$_2$-agonists causes major rebound hypertension, which is best treated by reinstituting therapy. Clonidine is the only transdermal antihypertensive agent available in the USA.

Direct arterial vasodilators (hydralazine and minoxidil) have been in clinical use for many years, acting by causing vascular wall smooth muscle relaxation. As a result of 'direct' vasodilation, they cause reflex tachycardia and promote fluid retention. Therefore, direct vasodilators should always be used in conjunction with beta-blockers (to block the tachycardia) and diuretics (to counter the fluid retention). Hydralazine and minoxidil cause activation of sympathetic tone, and minoxidil causes greater fluid retention.

Direct vasodilators should be reserved for patients with resistant hypertension. Accordingly, they are typically used as third-line therapy or higher, as hydralazine was used in ALLHAT. Hydralazine is typically limited to 300 mg/day because of the risk of systemic lupus. Minoxidil causes hirsuitism and is therefore not well-tolerated by women.

Renal denervation therapy for resistant hypertension

Resistant hypertension is a difficult issue in clinical practice. Although precise statistics are not available, it is estimated that about 10–12% of patients with hypertension do not respond to treatment; hence the term resistant hypertension. When the BP level remains >140/90 mmHg for uncomplicated hypertension or >130/80 mmHg in patients with diabetes or CKD on optimal therapy with at least three antihypertensive drugs (including a diuretic), it is termed 'resistant hypertension'; the term is also applied to patients who require four antihypertensive

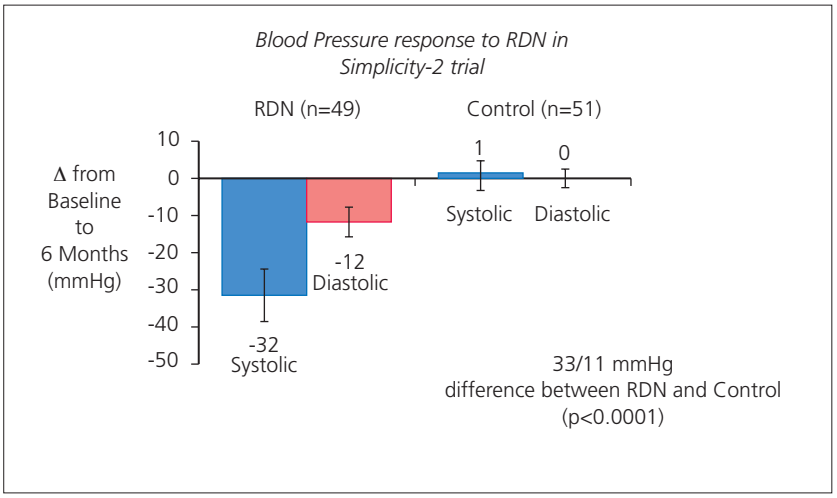


Fig. 5.4 Blood pressure response to renal denervation therapy in the Symplicity HTN-2 Trial. (Adapted from Ram CVS, Wali M (2013) Renal denervation in resistant hypertension: an emerging novel therapy. *J Clin Prev Cardiol* **2:**73–83.)

drugs to achieve the goal BP levels. Strictly, resistant hypertension is applicable only to patients who are compliant with prescribed therapy. Patients with resistant hypertension are at high risk for complications, excessive morbidity, disability, and premature mortality. Therefore, patients with resistant hypertension require special attention.

The traditional approach to treating resistant hypertension medically is to utilize a combination of conventional antihypertensive drugs at maximally tolerated doses. In many cases, after excluding etiological factors, direct vasodilators (hydralazine/minoxidil) are also tried as a component of combination therapy to manage resistant hypertension. One of the pathophysiological mechanisms attributed to resistant hypertension is excessive activity of the SNS. It has become apparent in recent years that renal afferent and efferent output affects SNS activity and contributes to hypertension. Both the afferent and efferent pathways between the renal artery and brain exacerbate the activity of the SNS, resulting in the development of hypertension.

Interruption of the connection between brain sympathetic activity and the kidney has been shown to lower BP. Disruption of the renal afferent and efferent nerve traffic lowers the BP. A new novel technique (renal denervation [RDN] therapy) has been shown to improve BP substantially in hypertension. Using a catheter, low frequency ablation of renal nerves is accomplished in a safe manner to control resistant hypertension. RDN as a method of controlling resistant hypertension is currently undergoing extensive investigation; the results so far are promising (Figure 5.4). Further experience and additional clinical trials will yield evidence about the future value of RDN in the clinical management of patients with resistant hypertension.

Acknowledgement

The author thanks Dr William J Elliot MD, PhD for his advice and participation in the writing of this chapter.

CHAPTER 6

6

HYPERTENSIVE EMERGENCIES AND URGENCIES

Overview

All forms of hypertension can be complicated by a hypertensive crisis, determined primarily by the absolute level of BP and the rapidity (abruptness) with which the critical level is reached. Therapy in such crises is dictated mainly by the resultant or imminent complications (e.g. aortic dissection, heart failure) rather than by the absolute BP.

Etiology

Hypertensive crises are, by convention, categorized into emergencies and urgencies (*Tables 6.1 and 6.2*), but this distinction is arbitrary. Hypertensive emergencies carry a poor prognosis unless the BP level is reduced immediately – generally within a few hours from onset – whereas hypertensive urgencies pose less immediate danger, requiring BP reduction over several hours or days. However, there is no definitive level of BP that separates a hypertensive emergency from an urgency. In fact, the clinical presentation is the basis on which the treating physician makes such a distinction.

Table 6.1. Examples of hypertensive emergencies.

- Accelerated/malignant hypertension
- Hypertensive encephalopathy
- Acute left ventricular failure
- Acute aortic dissection
- Intracranial hemorrhage
- Pheochromocytoma crisis
- Monoamine oxidase inhibitor plus tyramine interaction
- Eclampsia
- Substance/drug-induced acute hypertension

Table 6.2. Examples of hypertensive urgencies.

- Accelerated/malignant hypertension
- Severe hypertension associated with coronary artery disease
- Severe hypertension in the organ transplant patient
- Preoperative hypertension
- Hypertension associated with burns
- Severe, uncontrolled hypertension

Hypertensive emergencies

Accelerated and malignant phases of hypertension

Although the term 'malignant' hypertension is imprecise, it has striking pathological characteristics consisting of microvascular and vascular lesions in the kidney and organs that are particularly vulnerable to acute BP elevation. Clinically, the lesions of accelerated hypertension are best seen in the retina (hypertensive retinopathy) in the form of exudates, hemorrhages, and arteriolar spasm, but without papilledema. Malignant hypertension is an an extension of the accelerated form and is distinguished by the additional presence of papilledema (Figure 6.1).

The BP level in malignant hypertension is usually very high, with diastolic levels often exceeding 130–140 mmHg, but the degree of BP elevation is not a reliable criterion. It is the extent of vascular injury that determines the nature of malignant hypertension. Severe headache is a common symptom of malignant hypertension, often associated with symptoms ranging from blurring to blindness, drowsiness, and altered mental status. CHF is a complication of malignant hypertension as a direct consequence of left ventricular dysfunction or because of rapid volume retention from associated renal failure. Azotemia is common and can be associated with proteinuria. Renal function deteriorates rapidly without immediate therapeutic intervention, and even with treatment it may not improve in some patients. Patients with accelerated/malignant hypertension should be treated in the hospital, preferably in an intensive care unit. If there is no significant target organ dysfunction, they may be managed on the wards with close supervision.

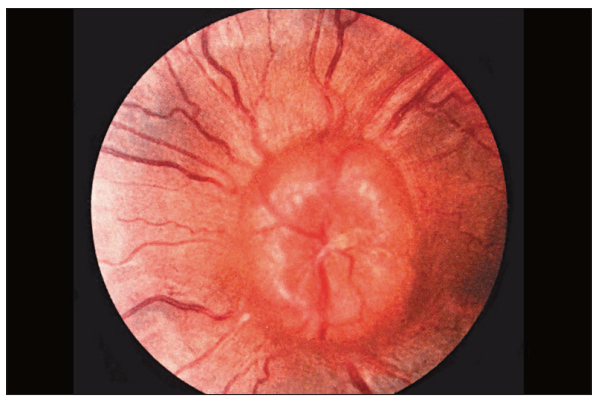


Fig. 6.1 Fundoscopic image of papilledema in malignant hypertension.

Although parenteral therapy is widely used in the initial treatment of malignant hypertension, several oral therapies can also be successfully used. ACE inhibitors, minoxidil, clonidine, prazosin, labetalol, and nifedipine have all been used for the initial treatment of malignant hypertension. The choice between oral and parenteral therapy depends on the monitoring facilities, the condition of the patient, and coexisting complications.

Hypertensive encephalopathy

Hypertensive encephalopathy is an uncommon but serious complication of severe hypertension. Although hypertensive encephalopathy occurs mainly in patients with chronic uncontrolled or malignant hypertension, it can also complicate sudden hypertension of short duration. Hypertensive encephalopathy should be rapidly diagnosed and treated, as it carries a poor prognosis when left untreated. The clinical manifestations of hypertensive encephalopathy are due not only to the severity of BP elevation, but also to the abrupt onset of hypertension in a previously (relatively) normotensive individual. The condition occurs more frequently against the background of renal insufficiency. The full clinical manifestations of hypertensive encephalopathy may take 12–48 hours to evolve.

Severe generalized headache is a prominent symptom. Other symptoms such as confusion, somnolence, and stupor may appear simultaneously with or following the onset of headache. The patient may be quite restless during the initial stages of the syndrome. Other clinical features may include projectile vomiting, visual disturbances ranging from blurring to frank blindness, and transient focal neurological deficits. In children, generalized or focal seizures may be the principal clinical manifestation of hypertensive encephalopathy.

On physical examination the BP is invariably elevated, but there is no fixed level of BP above which encephalopathy is likely to occur. The fundi reveal generalized arteriolar spasm with exudates/hemorrhages. Papilledema is present in most patients with hypertensive encephalopathy.

Hypertensive encephalopathy must be differentiated from other acute neurological complications of hypertension such as cerebral infarction, intracerebral hemorrhage (Figure 6.2) and uremic encephalopathy. The only definitive way to confirm the diagnosis of hypertensive encephalopathy is by a prompt response to immediate antihypertensive therapy.

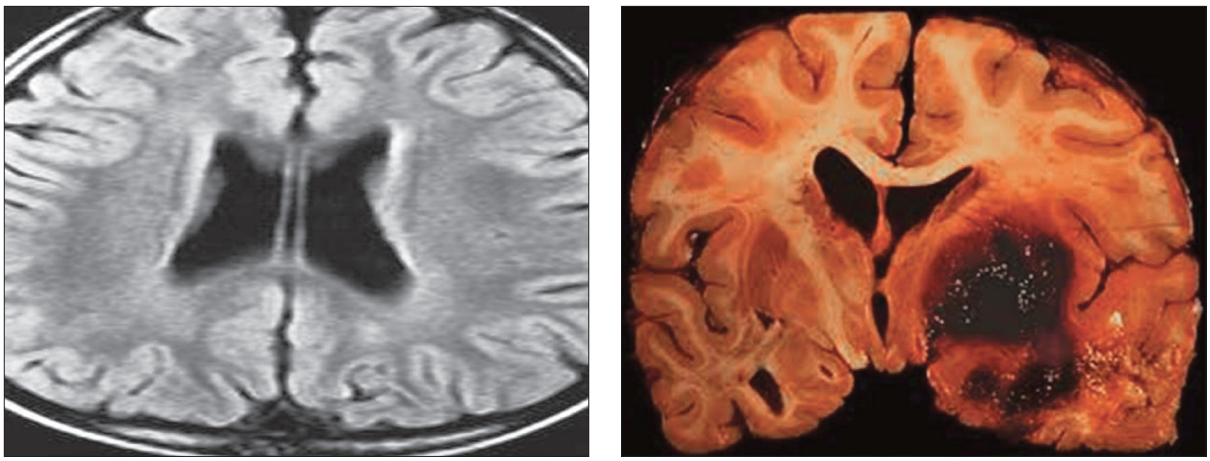


Fig. 6.2 Hypertensive intracerebral hemorrhage on CT scan (left) and pathological appearance (right).

Once hypertensive encephalopathy is suspected, the BP should be lowered quickly, although the diastolic BP should probably be allowed to remain at or slightly above 100 mmHg.

Severe hypertension and stroke syndromes

Patients with acute cerebrovascular (stroke) syndromes and severe hypertension pose a therapeutic dilemma. When intracerebral pressure rises as a result of hemorrhage or thrombotic infarction, cerebral blood flow may no longer be autoregulated. Therefore, reduction in the systemic BP can further compromise cerebral blood flow. If severe hypertension is allowed to persist, however, the stroke may worsen. In many patients with acute stroke, initial (reflexive) hypertension may resolve spontaneously within 48 hours. There are no definitive published data that provide clinical guidance in managing patients with acute stroke and hypertension.

Based on the known pathogenesis of stroke, especially if there is intracerebral hemorrhage, it is reasonable to reduce the BP to near-normal levels, yet to a degree that will not compromise cerebral function. If there is evidence of progression of the disease or worsening of the neurological manifestations with BP lowering, there should be a reassessment of the therapeutic approach. Precautions should be taken to avoid hypotension in these patients and it is advisable not to lower the diastolic BP to less than 100 mmHg. Generally, the reduction should be no more than 20% of the baseline BP level. Although a conservative approach to lowering the BP in patients with acute stroke has been standard therapy for many years, recent clinical studies suggest significant positive outcomes in acute stroke syndromes with prompt and immediate lowering of BP.

Acute aortic dissection

Among the symptoms listed in *Table 6.3*, severe pain is the most frequent manifestation of acute aortic dissection. The pain of aortic dissection can be confused with the pain of acute MI, although there are certain subtle differences between the two conditions. The pain of dissection is abrupt in onset and is severe at onset, whereas patients with acute MI often report a more gradual escalation of pain. The pain of MI may come and go, whereas aortic dissection pain occurs abruptly and is constant. Certain descriptions, such as tearing, lacerating, throbbing, ripping, excruciating, and burning, have been used by patients experiencing acute aortic dissection.

As soon as the diagnosis of acute aortic dissection is apparent (Figures 6.3 and 6.4), if the patient is hypertensive, BP should be reduced to near-normal levels with a drug that causes the BP to come down smoothly rather than drastically. Direct vasodilators that cause reflex stimulation of heart rate are contraindicated in acute aortic dissection. When considering medical therapy, it should keep in mind that the force and velocity of ventricular contraction (dp/dt [force/velocity]) and the pulsatile flow are important determinants of the shearing force acting on the aortic wall. Attempts should be made to decrease the dp/dt with rapidly acting cardiovascular drugs.

Trimethaphan, a ganglion-blocking agent, was widely used in the past for medical management of acute aortic dissection, but is no longer recommended as the initial drug of choice. Trimethaphan is not generally available and many clinicians are not experienced in its use. Other therapies should be employed and these include labetalol (a combined alpha- and beta-blocking drug) or esmolol (an ultra-short acting beta-blocker) in combination with sodium nitroprusside.

Table 6.3. Clinical features of acute aortic dissection.

- Severe pain in the chest, intrascapular region, neck, midback, sacral area
- Syncope
- Confusional state or headache
- Blindness
- Hemoptysis
- Dyspnea
- Nausea and vomiting
- Melena or hematemesis

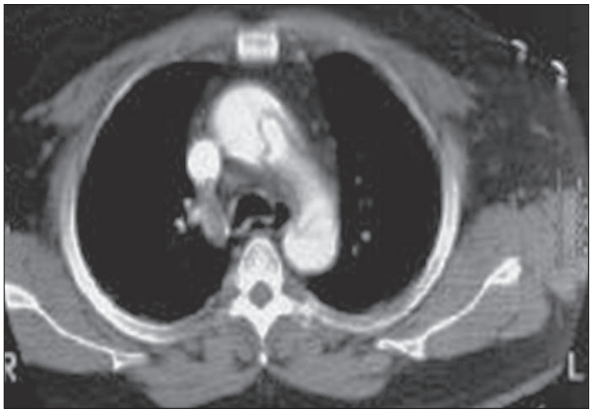


Fig. 6.3 CT scan showing both proximal and distal dissection of the aorta.

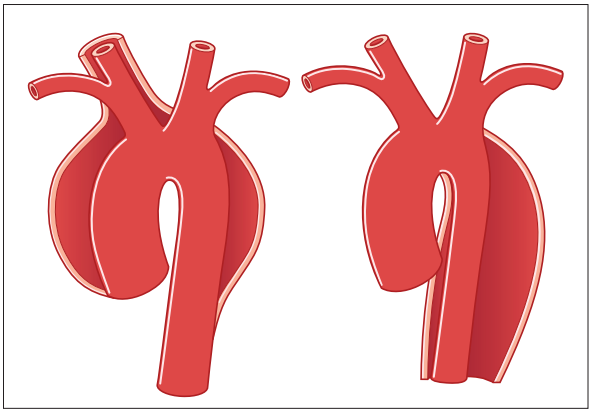


Fig. 6.4 Anatomical types of aortic dissection - ascending (left) and descending (right).

Acute pulmonary edema

Severe hypertension may cause or precipitate acute left ventricular failure (Figure 6.5); the higher the BP, the harder the left ventricle must work. In acute pulmonary edema, myocardial oxygen requirements increase due to increased end-diastolic fiber length and and increased end-diastolic volume. Such changes in cardiac function are particularly detrimental in the presence of coronary artery disease, requiring prompt reduction of BP with a balanced vasodilating agent such as nitroprusside. Sodium nitroprusside decreases both preload and afterload pressures, with restoration of myocardial function and CO. Although ACE inhibitors, by virtue of their pharmacological actions, may be useful in this situation, there is little clinical experience concerning the acute therapeutic response to ACE inhibition in patients with acute left ventricular failure.

Severe hypertension associated with acute myocardial ischemia

Systemic hypertension increases myocardial oxygen consumption by increasing left ventricular myocardial wall tension. Conceptually, patients with MI and severe hypertension are likely to benefit from BP reduction, but there are no conclusive data proving this concept. Reduction of systemic BP reduces cardiac work, wall tension, and oxygen demand and thus could limit myocardial necrosis in the early phase of infarction. With an afterload pressure reduction, hemodynamic status may improve significantly in acute MI.

In the West Birmingham Study, patients with malignant hypertension were demonstrated to have significant cardiac hypertrophy associated with systolic dysfunction, impaired relaxation, and dilated left atria, irrespective of the duration of hypertension, thereby predisposing to cardiovascular complications including heart failure and cardiac arrhythmias such as atrial fibrillation and sudden death. These findings emphasize the importance of prompt recognition and early treatment of malignant hypertension.

Pheochromocytoma crisis

Pheochromocytoma hypertensive crisis may present with dramatic clinical features, including marked BP elevation, profound sweating, rapid sinus tachycardia, atrial and ventricular dysrhythmias, chest pain (due to myocardial ischemia), pallor, numbness, tingling, and coldness of the feet and hands. A single paroxysmal attack lasts from a few minutes to hours and may occur as often as several times a day to once a month or less. A pheochromocytoma crisis is particularly dangerous in patients with other cardiovascular comorbidities, such as coronary artery disease and ascending aortic aneurysms.

When pheochromocytoma is suspected, the alpha-adrenergic blocking drug phentolamine is specific for this condition and (if available) should be given at a dose of 1–5 mg intravenously, repeated in a few minutes if needed. An alternative to phentolamine is sodium nitroprusside, but it is less specific. A beta-blocking drug may be useful in the presence of cardiac arrhythmia, but administration of

beta-blocking agents in this setting should **always** be preceded by either phentolamine or phenoxybenzamine. Beta-blockade, if given alone, can aggravate unopposed alpha-mediated peripheral vasoconstriction, therefby further perpetuating the hypertension. Labetalol, a combined alpha- and beta-receptor blocking drug, has also been advocated for this condition, but in the author's experience its efficacy is inconsistent in controlling clinical manifestations of pheochromocytoma.

Clonidine withdrawal syndrome

Abrupt discontinuation of high doses of clonidine may cause a hyperadrenergic physiological state resembling pheochromocytoma. Clonidine stimulates alpha receptors in the brainstem, thereby reducing peripheral sympathetic activity. When clonidine (in high doses) is abruptly discontinued or rapidly tapered, a syndrome has been identified that consists of nausea, palpitations, anxiety, sweating, nervousness, and headache, along with marked elevation of BP.

Symptoms of clonidine withdrawal can be managed by reinstitution of clonidine. If there is marked elevation of BP and the patient is experiencing symptoms such as palpitations, chest discomfort, and epigastric discomfort, intravenous administration of phentolamine or labetalol may be necessary.

Cocaine-induced hypertensive crisis

Cocaine can cause an abrupt sudden increase in systemic BP and heart rate, resulting in a hypertensive emergency. Neurohumoral factors triggered by cocaine likely cause intense vasoconstriction, thus increasing vascular resistance and BPl. A sudden rise of BP in a previously normotensive individual may precipitate a serious cardiovascular complication, necessitating rapid lowering of the BP. Aortic dissection and even spontaneous acute coronary dissection have been reported after cocaine abuse, presumably due to sudden BP elevation.

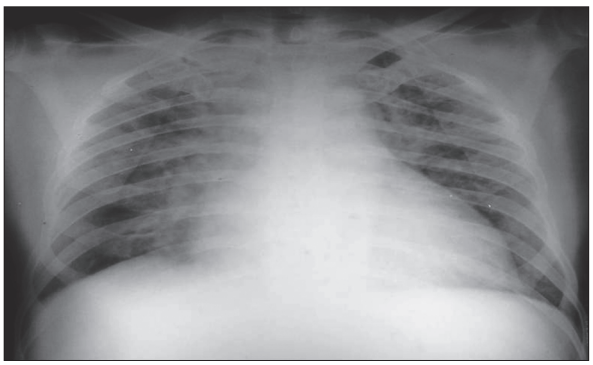


Fig. 6.5 Chest radiograph showing congestive heart failure in a patient with malignant hypertension.

Eclampsia

Eclampsia is a potentially serious cardiovascular complication of pregnancy. The definitive therapy is delivery of the baby. In addition, the BP should be reduced to prevent neurological, cardiac, and renal damage. Although other antihypertensive drugs may be effective in reducing the BP, the agent of choice for rapid control of severe hypertension is hydralazine, which has a long record of safety. Animal studies have shown that nitroprusside can cause fetal complications and its use should be reserved for hypertension refractory to hydralazine or methyldopa. The ganglion-blocking drug trimethaphan should be avoided because of the risk of meconium ileus. In pregnancy-induced hypertension, volume depletion may be present and diuretics should be avoided. ACE inhibitors and ARBs should be avoided because of possible fetal/placental toxicity. Magnesium sulfate is effective adjunctive therapy to control seizures. Eclampsia and pre-eclampsia are covered in more detail in Chapter 7 (Hypertension in pregnancy).

Guidelines for treating a patient with a hypertensive crisis

Overview

The need to hospitalize, therapeutic options, and questions of parenteral versus oral therapy depend on the clinical status of the patient and the available facilities. Patients with hypertensive emergencies should be hospitalized, while those with hypertensive urgencies may not always require hospital admission. The therapeutic concept underlying management of a hypertensive emergency is not only to lower the BP quickly, but to prevent, arrest, and reverse TOD. Although there are no specific guidelines for the degree of desired BP reduction, a reasonable goal for most hypertensive emergencies is to lower the diastolic BP to 100 mmHg (or to reduce the mean arterial pressure by 20%) over a period of minutes to hours.

Parenteral therapy for treatment of hypertensive emergencies (*Table 6.4*)

Nitroprusside

Sodium nitroprusside is a potent, rapidly acting intravenous drug with rapid onset and offset of action. The initial infusion rate is 0.25–10 µg/kg/minute, which can be increased every five minutes until the desired BP is obtained. After the desired BP is reached with nitroprusside infusions, the BP should be continuously monitored. Thiocyanate toxicity from nitroprusside, although extremely rare, may occur. Prophylactic infusion of hydroxocobalamin (vitamin B_{12a}) at 25 mg/hour decreases cyanide concentration and tissue hypoxia resulting from nitroprusside infusion during surgery, but this compound is not routinely available. Thiocyanate toxicity secondary to nitroprusside is uncommon and occurs only with high doses

of nitroprusside in the presence of renal failure. Treatment should be interrupted when the thiocyanate level is close to 10 mg/dl. Monitoring of plasma thiocyanate levels is not mandatory as long as the patient's clinical status is closely assessed and there is adequate renal function. Treatment of thiocyanate toxicity requires discontinuation of the drug and instituting dialysis.

Table 6.4. Parenteral drugs used for hypertensive emergencies.

Drug	Doses	Route of administration	Onset of action	Duration of action	Adverse effects	Comments
Sodium nitroprusside	0.25–10 µg/kg/minute. Maximum dose of no more than 10 µg/kg/minute	IV infusion	Within 30 seconds	1–2 minutes	Hypotension, nausea, vomiting, muscle twitching, thiocyanide and cyanide intoxication, methemoglobinemia	Most hypertensive emergencies; use with caution in patients with renal and hepatic insufficiency and high intracranial pressure
Fenoldopam	0.1–0.6 g/kg/minute	IV infusion	4–5 minutes	10–15 minutes	Reflex tachycardia, may raise intraocular pressure, headache and nausea	Renal insufficiency, peri- and postoperative control of BP
Nitroglycerine	5–100 µg/minute	IV infusion	2–5 minutes	3–5 minutes	Headache, nausea, vomiting, tolerance with prolonged use	Coronary insufficiency
Nicardipine	5–15 mg/hour	IV infusion	5–10 minutes	1–4 hours	Reflex tachycardia, headache, nausea, vomiting, flushing	Most hypertensive emergencies, caution with heart failure
Hydralazine	10–20 mg IV 10–50 mg IM	IV infusion IM injection	10–20 minutes	4–12 hours	Reflex tachycardia, headache, nausea, vomiting, aggravation of angina	Eclampsia, caution with high intracranial pressure
Enalaprilat	1.25–5 mg q6h	IV infusion	10–15 minutes	6–24 hours	Hypotension, renal failure	Acute left ventricular failure
Labetolol	20–80 mg IV bolus every 10 minutes; 2 mg/minute infusion	IV bolus IV infusion	5 minutes	3–6 hours	Nausea, vomiting, bronchospasm, heart block, orthostatic hypotension	Most hypertensive emergencies except heart failure
Phentolamine	5–10 mg/minute	IV bolus	1–2 minutes	3–5 minutes	Reflex tachycardia, headache	Pheochromocytoma

Intravenous labetalol

Labetalol is a combined alpha- and beta-adrenergic blocking drug that can be used for parenteral or oral treatment of hypertensive emergencies. Intravenous labetalol administered as either continuous infusion or bolus injections promptly reduces BP because of its rapid onset of action. Controlled smooth reduction in BP is attained by continuous infusion of labetalol at the rate of 0.5–2.0 mg/minute. Rapid (but not abrupt) lowering of BP is also accomplished with bolus injections of labetalol. Labetalol should not be given to patients who have contraindications to beta blockers, including severe heart failure, atrioventricular conduction block, asthma, and chronic obstructive pulmonary disease.

Intravenous nicardipine

Nicardipine is a DHP calcium antagonist that exerts a prompt hypotensive effect when given intravenously to patients with severe hypertension. Nicardipine infusion is started at 5.0 mg/hour, and can be gradually titrated upward to obtain the desired therapeutic effect. Once a stable BP level is reached, further dose alterations are generally not necessary. Because of its mechanism of action (calcium channel blockade), nicardipine may be beneficial in preserving tissue perfusion, which is particularly advantageous in patients with ischemic disease. In the author's clinical experience, nicardipine is a useful option in the immediate management of severe hypertension.

Trimethaphan

Trimethaphan camsylate is a ganglion-blocking agent and is the drug of choice for the medical treatment of acute aortic dissection. As with nitroprusside, trimethaphan should be administered as a continuous intravenous drip, and constant monitoring is necessary, preferably in the intensive care unit. The usual starting dose of the drug is 1 mg/minute titrated to obtain the desired BP level. After prolonged infusion, tachyphylaxis may result due to intravascular volume expansion, which can be partially overcome by effective diuretic therapy. Trimethaphan is not readily available for clinical use.

Hydralazine

The antihypertensive action of hydralazine results from direct relaxation of the vascular smooth muscle, and is accompanied by reflex increases in stroke volume and heart rate, which can precipitate myocardial ischemia. Intramuscular or intravenous administration of hydralazine results in an unpredictable but definite fall in BP. For treating hypertensive emergencies, the initial dose should be 10–20 mg. The onset of the hypotensive effect occurs within 10–30 minutes and its duration of action ranges from 3 to 9 hours. The dose and frequency of administration necessary to control BP are highly variable. The delayed onset and the unpredictable degree of the hypotensive effect are problematical. For these reasons, hydralazine therapy is only clinically relevant in the treatment of eclampsia.

Phentolamine

Phentolamine is an alpha-receptor-blocking agent and is specifically indicated for treating hypertensive crises associated with increased circulating catecholamines. These include pheochromocytoma crisis, certain cases of clonidine withdrawal syndrome, and crises resulting from monoamine oxidase inhibitor and drug–food interaction. The hypotensive effect of a single intravenous bolus injection is short lived and lasts less than 15 minutes. Phentolamine is not easily available for unanticipated clinical use.

Nitroglycerin

Nitroglycerin is a weak systemic arterial dilator with a significant effect on large arteries rather than on smaller arteries. Low doses cause venodilation; much higher doses are required to produce a fall in systemic BP. Because of its pharmacological actions, nitroglycerin infusion may be particularly beneficial in patients with coronary artery disease with or without hypertension. Isosorbide dinitrite therapy has also been used for immediate treatment of severe hypertension, but its precise role and guidelines for administration are not fully delineated.

Fenoldopam

Fenoldopam is the first dopamine (DA_1) receptor agonist approved for clinical use. The dopaminergic receptors DA_1 and DA_2 exert important physiological actions on various vascular beds, which is the reason for extensive study of these receptors as targets of pharmacotherapy. DA_1 receptors are juxtaposed post-synapses on the vascular smooth muscle. Stimulation of DA_1 receptors yields beneficial cardiovascular consequences such as systemic and renal vasodilation. Fenoldopam selectively and preferentially stimulates the DA_1 receptor, resulting in vasodilation. Intravenous infusion of fenoldopam causes a dose-related fall in systemic BP, mainly due to vasodilation and, to a small extent, to natriuresis. Poor and variable absorption and erratic bioavailability precluded the development of oral fenoldopam. The drug should be given as an infusion, not as a bolus.

Experimental studies in patients with a moderate degree of hypertension have clearly established the useful antihypertensive effects of fenoldopam. In severe forms of hypertension (diastolic BP >120 mmHg), fenoldopam infusion produces dramatic antihypertensive effects. Fenoldopam efficacy is similar to that of nitroprusside, a 'gold standard' drug for rapid BP lowering. However, in contrast to nitroprusside, fenoldopam acutely improves renal function parameters such as creatinine clearance and sodium excretion. An increase in renal blood flow has also been demonstrated with fenoldopam. In some settings, fenoldopam may be more advantageous than nitroprusside because of its possible target organ protection.
A number of the minor adverse effects of fenoldopam are due to its vasodilatory actions, including sinus tachycardia, flushing, and headache. These side-effects may appear at the start of fenoldopam infusion and often dissipate. Non-specific electrocardiographic ST-T changes are probably due to systemic hemodynamic changes caused by fenoldopam, but not to direct cardiac effects. Fenoldopam increases intraocular pressure and should be avoided in patients with glaucoma. No adverse interactions have been reported between fenoldopam and other cardiovascular drugs.

Role of concomitant diuretic therapy in the management of hypertensive emergencies

Diuretics *per se* have a limited role in the management of hypertensive emergencies; however, they potentiate the therapeutic response to non-diuretic agents. When BP does not respond satisfactorily to an adequate dose of primary antihypertensive drug, addition of a diuretic (e.g. furosemide) may be helpful. In volume overload states such as heart failure, concomitant administration of a loop diuretic is definitely indicated for optimal results. Diuretics, however, should not be used routinely in the management of hypertensive crises because prior volume depletion may be present in some patients with severe or complex hypertension. The need for diuretic therapy should therefore be individualized on the basis of the patient's hemodynamics and renal function.

Oral therapy for acute treatment of severe hypertension

Clinical experience has shown that antihypertensive drugs given orally in either single or multiple doses lower the BP immediately in patients with severe hypertension. Oral therapy, however, is appropriate for patients with hypertensive urgencies, not emergencies.

Nifedipine

Nifedipine, a CCB, given orally or sublingually, reduces BP rapidly and is useful in the management of hypertensive crises. Immediate reduction in BP can be accomplished with sublingual (punctured capsule, or nifedipine liquid drawn out of the capsule with a syringe) or oral administration of the capsules. Nifedipine is also effective when the capsule is bitten and swallowed. The advantages of nifedipine are rapid onset of action and lack of central nervous system depression. Nifedipine may cause reflex sinus tachycardia. Because the duration of action of nifedipine is short, patients who receive this drug for hypertensive emergencies should be monitored for several hours, for possible readministration of the drug. An abrupt fall in BP induced by nifedipine can cause certain adverse effects (symptomatic hypotension, tachycardia, and ischemic events), which are occasionally life-threatening. For this reason, use of nifedipine capsules has been virtually eliminated in clinical practice.

Clonidine

Clonidine produces an immediate antihypertensive effect with repetitive dosing. Typically, clonidine loading is accomplished in the emergency department by oral administration at the rate of 0.1 mg/hour until the desired BP is obtained. Clonidine loading is used less often than in the past, mostly due to its unfavorable side-effects profile and the availability of safer and more efficacious oral agents.

Angiotensin-converting enzyme inhibitors

Captopril, an ACE inhibitor, is effective in the immediate treatment of severe hypertension and hypertensive crisis. Captopril lowers BP promptly without causing tachycardia and, therefore, offers a distinct hemodynamic advantage over direct arteriolar dilators. However, the maximal effect from orally-administered captopril may not be attained for as long as two hours. There are, however, some reports documenting the effectiveness of sublingual captopril in treatment of hypertensive crises. Because experience with sublingual captopril is limited, further data are needed for a clear definition of its role in the acute management of hypertensive crisis.

Minoxidil

Minoxidil is a powerful direct vasodilator and is efficacious in the treatment of refractory or severe hypertension. Because of its relatively rapid onset of action and sustained duration, minoxidil can be used for the treatment of hypertensive crises. Minoxidil in doses ranging from 2.5 to 10 mg can be given every 4–6 hours initially in the treatment of severe hypertension. Minoxidil works best when given along with a diuretic, and an adrenergic blocker is necessary to counteract the reflex tachycardia.

Oral labetalol

Labetalol, a combined alpha- and beta-adrenergic blocker, can be administered orally (100–300 mg) in the treatment of hypertensive urgencies. Because of its dual adrenergic blockade, the fall in BP is not accompanied by reflex tachycardia, which is especially beneficial in patients with coronary artery disease.

Conclusion

Once the hypertensive emergency has resolved and the patient's clinical condition is stable, the physician should investigate factors that might have contributed to the dangerous elevation of BP, such as non-compliance to prescribed therapy or the presence and/or progression of a secondary form of hypertension (e.g. renal artery stenosis or pheochromocytoma). After the patient's condition has stabilized, the clinician should arrange for long-range and periodic outpatient follow-up plans. Close follow-up is essential for these patients.

The most important decision in the management of hypertensive emergencies is to assess the patient's clinical state and to ascertain whether the condition truly needs immediate reduction of BP. The choice of oral versus parenteral drug depends on the urgency of the situation, as well as the patient's general condition. The level to which the BP should be lowered varies with the type of hypertensive crisis and should be individualized. The choice of parenteral drug is dictated by the clinical manifestations and concomitant medical problems. There is no predestined level for the goal of acute hypertension therapy. Complications of therapy, mainly hypotension and ischemic brain damage, can occur in patients given multiple potent antihypertensive drugs in large doses. Perioperative severe hypertension should be treated carefully to prevent cardiovascular complications.

Future therapeutic progress to treat severe hypertension rapidly will involve evaluating the pharmacological role of a new generation CCB, clevidipine. In the author's view, a relatively asymptomatic patient who presents with severe hypertension (i.e. a diastolic BP of 130–140 mmHg) need not be treated with parenteral drugs. These patients should be managed on an individual basis and the usual course is to intensify or alter the previous antihypertensive therapy. Too often, asymptomatic patients and patients without acute problem are unnecessarily subjected to immediate and unnecessary therapy. Indiscriminate use of drugs such as nifedipine and furosemide should be strongly discouraged. Prevention of recurrent hypertensive emergencies is of considerable importance and requires aggressive and sustained control of chronic hypertension in the community.

CHAPTER 7

HYPERTENSION IN PREGNANCY

Overview

Normal fetal gestation entails many maternal hormonal and hemodynamic changes that affect BP. Placental development and fetal growth also cause maternal weight gain. In a normal pregnancy, BP falls during the first two trimesters, mostly due to changes in vascular tone. During the third trimester of pregnancy, BP will return to pre-pregnancy baseline levels.

About 10% of mothers are hypertensive during pregnancy, one-half of whom are already hypertensive before pregnancy and one-half develop high BP during gestation. Hypertension in pregnancy is classified depending on the time of onset of BP elevation and symptoms that signal TOD (*Table 7.1*). BP elevation during pregnancy is often mild and return to normal after delivery. Such transient, mild hypertension usually requires careful monitoring but no or minimal treatment. Some pregnancy-related hypertension, however, is dangerous to the mother and/or the fetus and requires treatment.

Table 7.1. Hypertension in pregnancy.

Chronic hypertension	BP greater than 140/90 mmHg before pregnancy or before the 20th week of gestation
Gestational hypertension	Hypertension after the 20th week without proteinuria. It includes women with pre-eclampsia who have not yet developed proteinuria and those with hypertension only. In the latter group, by 12 weeks post partum BP may either return back to normal or fail to normalize, leading to diagnoses of transient and chronic hypertension, respectively
Pre-eclampsia/ eclampsia	Hypertension after the 20th week with proteinuria. Eclampsia features seizures occurring without other cause
Pre-eclampsia superimposed on chronic hypertension	Pre-eclampsia that develops in addition to pre-existing hypertension

Blood pressure regulation in pregnancy

A remarkable number of cardiovascular and renal changes occur in pregnancy. Normal levels of certain hormones also change, with estrogen and progesterone rising to very high levels, which will continuously rise throughout pregnancy. There are multiple cardiovascular adaptations as the body responds to various signals, including increased cardiac work to meet the demands of expanding circulating blood volume. In addition, the BP rises due to alterations in the hormonal and hemodynamic adaptations to pregnancy.

In the initial stages of pregnancy, BP usually falls, which may mask mild pre-existing hypertension. Therefore, pre-existing hypertension or prehypertension may be manifest as an apparently normal BP in early pregnancy. Decreased BP is caused by decreased in vascular resistance (due to vasodilation), which begins in early stages of pregnancy and continues until the 32nd week. From that time on, SVR increases and the BP returns to near-normal levels. The decrease in vascular resistance is enough to offset the increased CO that occurs in this time frame. The result is a decreased BP as the fall in SVR outweighs the increase in CO.

Later in pregnancy, BP returns to near-baseline levels. The initial decrease in SVR is reversed in the second trimester. CO continues to increase during this time, partly due to plasma volume changes that begin during the 6th week of pregnancy. Blood volume may increase by as much as 50% during pregnancy, raising cardiac preload and, ultimately, stroke volume. Heart rate also increases during pregnancy with average resting heart rates 20 beats per minute faster than before pregnancy. The increased CO helps maintain circulation to the fetus and the greatly expanded maternal circulation. CO may rise by as much as 40% during pregnancy.

The RAAS helps regulation of maternal volume fluid and vascular resistance during pregnancy. The initial lower BP causes the kidneys to increase renin secretion and raises aldosterone levels. Renin levels may rise six-fold during pregnancy, due to the normal renal renin response to reduced BP, and to placental renin production and release. Increased levels of estrogen also contribute. Plasma renin increases vascular resistance through the vasoconstricting actions of AT II. Increased aldosterone raises fluid volumes through sodium retention and increased fluid retention also increases CO.

In normal pregnancy, responsiveness to AT is decreased by several mechanisms. The number of AT II receptors (AT_1) falls because of downregulation of receptor function. Vasodilators, such as nitric oxide, partially counteract vasoconstriction activity. Hormonal changes reduce the normal activity of the RAAS. Levels of progesterone are increased during pregnancy. One function of progesterone is to antagonize the activity of aldosterone and prevent excess sodium and volume retention.

Dangers of high blood pressure in pregnancy

Hypertension presents several dangers to the mother and fetus and is one of the main causes of maternal mortality during pregnancy. Changes associated with pre-eclampsia (PE) and eclampsia alter the kidneys, the central nervous system, and the vascular system. The risk of perinatal maternal mortality is more than three times greater for pregnant women with pre-existing hypertension than for

non-hypertensive mothers. Five percent of children born to mothers with pre-existing hypertension have low birth weight, which is linked to development of hypertension later in life. The severity of the hypertension contributes to the risk; mothers with severe hypertension are about two-fold more likely to have preterm births or reduced fetal growth compared with normotensive counterparts (Figures 7.1 and 7.2).

The dangers of hypertension are complicated by BP treatment because many antihypertensive drugs may cause significant risks to the fetus. All antihypertensive drugs enter the fetal circulation, and while all of these drugs have not been related to adverse fetal effects, some treatments remain controversial. This is discussed in detail later in this chapter.

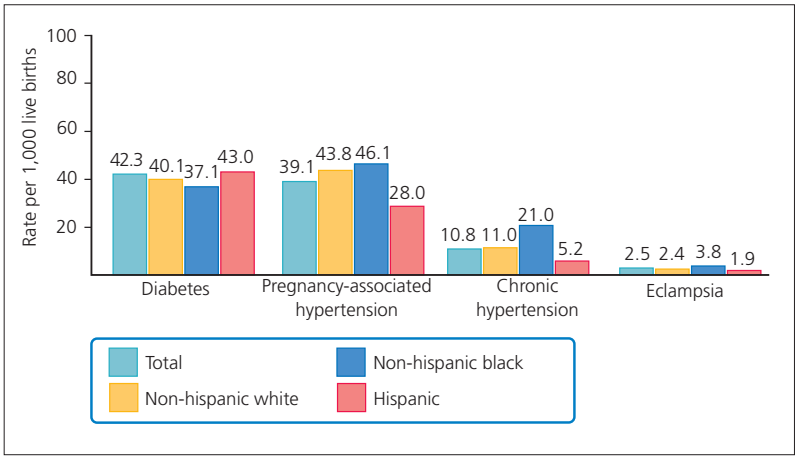


Fig. 7.1 Selected maternal morbidities and risk factors in pregnancy by maternal race/ethnicity, 2006. (Adapted from Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System.)

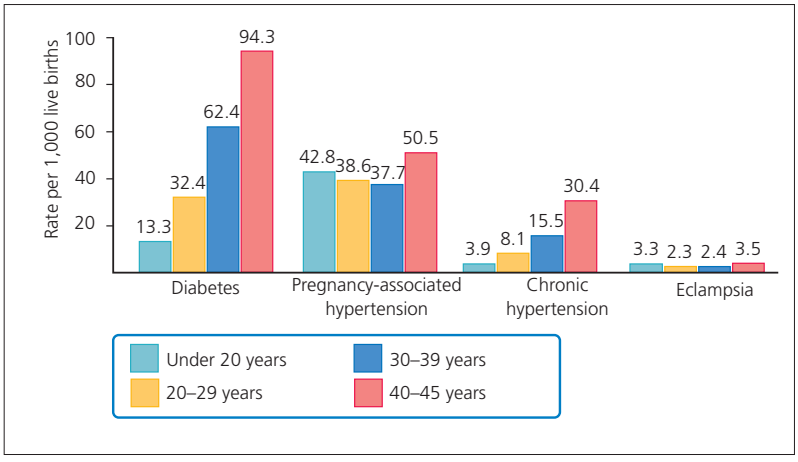
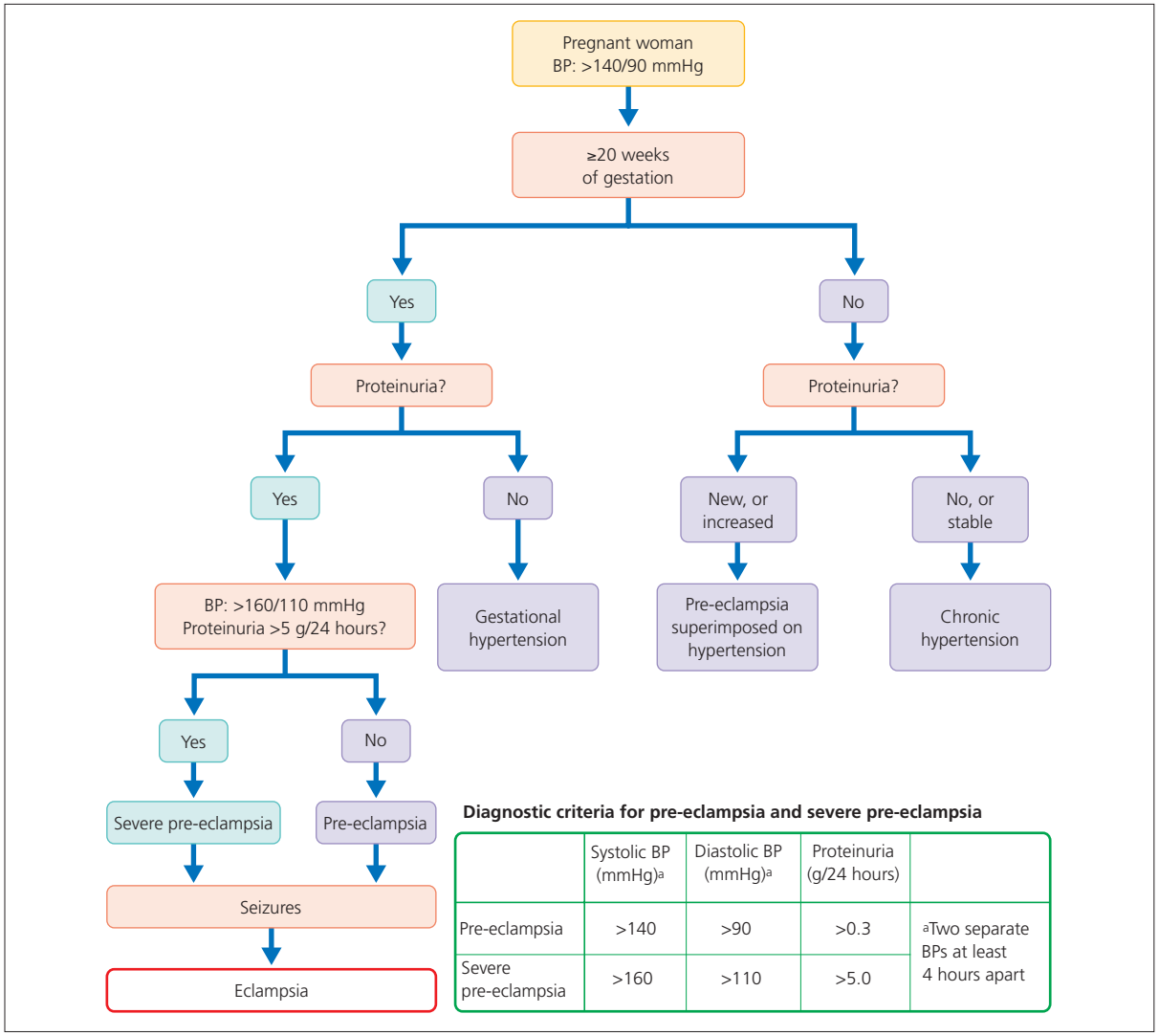


Fig. 7.2 Selected maternal morbidities and risk factors in pregnancy by maternal age, 2006. (Adapted from Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System.)

Pre-eclampsia/eclampsia

Definition

Pre-existing hypertension and gestational hypertension can be ragarded as primary hypertension that occurs during pregnancy. There are, however, different treatment recommendations because of concerns of fetal health, but the main concern is preventing complications of hypertension. PE and eclampsia are more systemic syndromes, which occur because the normal changes in pregnancy are significantly altered. Hypertension is only the first and most easily detectable sign, and many other aberrations remain undetected (Figure 7.3).



Diagnostic criteria for pre-eclampsia and severe pre-eclampsia

	Systolic BP (mmHg)[a]	Diastolic BP (mmHg)[a]	Proteinuria (g/24 hours)	
Pre-eclampsia	>140	>90	>0.3	[a]Two separate BPs at least 4 hours apart
Severe pre-eclampsia	>160	>110	>5.0	

Fig. 7.3 Overview of hypertension in pregnancy. (Adapted from Gilstrap L, Ramin S (2002) Diagnosis and management of preeclampsia and eclampsia. *ACOG Practice Bulletin. Clinical Management Guidelines for Obstetrician–Gynecologists* Number **33**; Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy (2000) *Am J Obstet Gynecol* **183:**S1–22; Block DR, Saenger AK (2010) Preeclampsia: prediction, diagnosis, and management beyond proteinuria and hypertension. *Clinical Laboratory News* **36(2)**.)

Possible pathogenesis and risks factors

The precise pathophysiology underlying PE or eclampsia is unknown. There are numerous theories that suggest a factor that might precipitate the development of PE, but none of these have been validated and convincingly demonstrated. There are several known risk factors associated with the development of PE (*Table 7.2*). A history of a prior episode of PE is associated with a seven-fold higher risk of developing PE during the next pregnancy. Risk is increased with the number of fetuses; for example, twins pose a risk three times greater for PE compared with a single fetus. General maternal health is also important. Primary hypertension, renal disease, and obesity are all risk factors for PE. A genetic link or predisposition is suggested by cases of PE among family members. Women with positive family histories of PE are three times more likely to develop PE. Disorders of the immune system also increase risk. Prior abortion, miscarriage, and blood transfusion are also risk factors for PE during the next pregnancy.

There is increasing evidence to suggest that the endothelium is abnormal in PE because some of the clinical features of PE can be explained by endothelial dysfunction. For example, elevated BP due to changes in vascular tone are determined by vascular smooth muscle responses to endothelial cell signaling. Another example of endothelial dysfunction resulting in the clinical signs of PE is altered vascular permeability, which leads to edema. Similar changes in the kidneys result in the development of proteinuria. Endothelial injury or very high levels of BP exacerbate vascular permeability.

Maternal and fetal factors contribute to initiation and progression of the disease state. Increased work load on the maternal cardiovascular system and changes in hormone levels alter the signaling pathways affecting endothelial cells, and angiogenesis is needed to vascularize the placenta. Endothelial dysfunction would impact negatively on these mechanisms and contribute to the development of PE and eclampsia.

Table 7.2. Risk factors associated with the development of pre-eclampsia.

- Multiple pregnancies
- Previous pre-eclampsia
- Family history
- Short interval between pregnancies
- Stress
- Low birth weight
- Previous abortion
- Previous miscarriage
- Previous blood transfusion
- Renal dysfunction
- Young age (<20 years old)
- Advanced age (>35 years old)
- Chronic hypertension
- Obesity
- Insulin resistance

Fetal contribution to hypertension is mainly through placental development. The best evidence for the role of the placenta in the pathogenesis of PE is supported by the following facts:

- PE always ends shortly after delivery of the placenta.
- Development of PE requires the presence of placental tissue, but not necessarily fetal tissue.
- If the placenta does not develop normally, hypoperfusion and ischemia may result.
- A placenta that displays hypoperfusion or ischemia releases numerous vasoactive factors that cause endothelial cell dysfunction.

Incorrect remodeling of the spiral arteries is thought to be one of the main contributors to abnormal placental development (Figure 7.4). In normal pregnancy, spiral arteries must develop from smaller conduits, with relatively restricted blood flow, into larger, lower resistance arteries that supply the greater nutrient needs of the placenta and fetus. Cytotrophoblast cells migrate to the placenta, traveling through many cell types, and contribute to the remodeling of the spiral arteries. If these cell types do not migrate far enough or fail to differentiate properly, spiral arteries will not form correctly, resulting in placental hypoperfusion.

There are several possible reasons for defective remodeling of spiral arteries and reduced nutrient exchange within the placenta. One possibility is that trophoblasts do not differentiate properly during migration and invasion. Differentiation of these cells is controlled by many different pathways that work to promote the correct cell type. As the trophoblast differentiates, the cell surface receptors and adhesion molecules change. If the trophoblast fails to receive proper signals or display proper cell surface proteins, incorrect differentiation occurs. Study of trophoblasts isolated from women with PE shows a reduction in adhesion molecules. This change would negatively affect cell differentiation and proper migration.

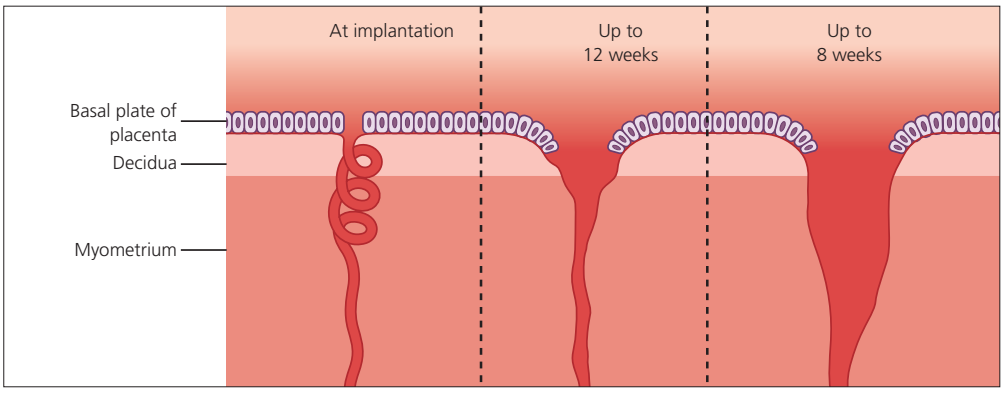


Fig. 7.4 Normal invasion of spiral arteries by trophoblasts converts them into deltas and so improves blood flow. This invasion is defective in pre-eclampsia. (Adapted from Chamberlain G (1991) Raised blood pressure in pregnancy. *BMJ* **302:**1454–1458.)

Initial placental hypoperfusion becomes more pronounced as pregnancy advances and the fetus grows. The timing of PE (post 20 weeks gestation) supports the placental hypoperfusion hypothesis. The increased risk of developing PE with increased number of gestations also supports the concept that a critical size of placenta is needed for PE to occur. Twins, for example, place a higher demand for placental activity than a single fetus.

Another theory predicts that an ischemic placenta releases apoptotic factors as well as debris from necrotic cells. The debris directly alters maternal signaling or leads to an inflammatory response that alters cardiovascular regulation. In addition, the placenta is an endocrine organ that provides hormonal signals during pregnancy, and alterations of these signals can lead to systematic maternal endothelial dysfunction. Because placental vascularization is so dependent on angiogenesis, any changes in normal maternal endothelial cell function can cause abnormal placental development. Conditions early in pregnancy that could cause decreased perfusion of the placenta will alter spiral artery maturation and lead to greater hypoperfusion.

Much of placental development requires new blood vessel formation or growth, therefore angiogenesis is important for pregnancy. Many factors regulate angiogenesis and changing the balance of these regulating factors will alter angiogenesis and lead to endothelial dysfunction. Studies have shown that ischemic placentas trigger the release of the anti-angiogenic factor sFlt-I, which plays a role in PE pathogenesis. There are likely other soluble growth factors involved in altering angiogenesis and causing endothelial cell dysfunction.

Clinical features and evaluation

The diagnosis of PE is made when the BP is greater than 140/90 mmHg after the week 20 of pregnancy and proteinuria is detected. The features of eclampsia are the same but with the addition of seizures. If hypertension appears after the week 20, but proteinuria is absent, then the most likely diagnosis is gestational hypertension. Chronic hypertension is hypertension present before pregnancy begins or which develops before week 20. Finally, PE can be superimposed upon chronic hypertension. This condition is suspected when there is a sudden increase in BP or there is development of proteinuria in a patient with chronic hypertension.

Although hypertension is the most easily detectable feature of PE, the maternal response to endothelial cell dysfunction is associated with several other clinical features. Many of these features can be detected by laboratory tests to support the diagnosis of PE. Elevated BP is usually the first sign of PE and is also the most common clinical sign. Proteinuria is the second clinical sign for the diagnosis of PE, and generally increases over time. A ‘dip stick’ test is often used as a rapid indicator of protein in the urine, but quantification is often required as proteinuria levels of 0.3 g/day are consistent with PE. Other indications of PE are reduced GFR, decrease by as much as 40% compared with normotensive individuals. Patients with PE may also have hypocalciuria or hyperuricemia.

TOD beyond the kidneys commonly signifies worsening of PE to a severe form or progression to eclampsia (*Table 7.3*). Pulmonary edema or elevated liver function tests both suggest involvement of other organ systems, indicating severe PE. Laboratory tests can also be used to follow hematological changes. For example, platelet turnover increases in PE, and when the platelet count falls below 100,000 or thrombocytopenia is detected, severe PE is present. Any signs of involvement of the brain or central nervous system, including blurred vision or headache, also signify severe PE. The occurrence of seizures establishes the diagnosis of eclampsia.

Diagnosis

Diagnosis of PE or eclampsia requires careful evaluation. Many other syndromes might share the clinical signs of elevated BP and proteinuria that characterize PE. Evaluation should determine if these clinical signs are manifestations of some other condition. If the diagnosis of PE is correct, the next step is to determine the severity, which includes serum hematocrit and total platelet count. It is also important to assess the condition and overall health of the fetus, especially for signs of fetal distress or reductions in fetal growth rate.

Management

Prevention of PE is difficult without a clear idea of the mechanism that triggers the disease. One strategy is to avoid known risk factors for PE. Pregnancy during teenage years, obesity, and prior primary hypertension are some of the conditions associated with increased risk of PE (*Table 7.2*). If pregnancy occurs in a high-risk mother, there is evidence that calcium supplementation may be beneficial; there is also some evidence that low doses of aspirin can reduce the risk. However, the effectiveness of these measures is uncertain.

Treatment goals for PE and eclampsia are to prevent complications to the mother and to the fetus. Pharmacological and non-pharmacological treatments are available to manage hypertension in pregnancy. In cases of mild PE, patients should be closely observed for disease progression. The laboratory tests performed

Table 7.3. Clinical signs that might signify severe pre-eclampsia.

- Hypertension
- Proteinuria (>0.3 g/day)
- Decreased GFR
- Pulmonary edema
- Elevated liver function tests
- Elevated serum creatinine
- Facial edema
- Weight gain (>2.3 kg [5 lb] per week)
- Low platelet count
- Blurred vision or headaches
- Seizures

as part of the evaluation can provide information about TOD and severity of the PE. The well-being and growth of the fetus should also be monitored. When PE is mild and stable, bed rest is generally prescribed. The true benefit of bed rest is uncertain, but it is traditionally recommended and still widely advocated.

Antihypertensive drugs are usually not recommended in cases of mild PE. Drugs may lower the BP, but there is no evidence that they provide any protective effect for PE or change disease progression. There is also no evidence that the morbidity or mortality related to PE is altered by treatment with antihypertensive drugs. Early delivery is one way to reduce the risk and is the only known way to cure PE.

Pharmacological intervention may be necessary when the BP becomes extremely high (diastolic 105 mmHg or higher) or when the BP rises rapidly in a short period of time. This goal of pharmacological treatment is to limit maternal TOD and fetal damage due to high BP or severe PE. Some drugs, such as RAAS inhibitors, are contradicted in pregnancy. *Table 7.4* lists several drugs that may be used for treating severe hypertension according to recent recommendations of the National High Blood Pressure Education Program Working Group.

For cases of severe PE, preventing maternal or fetal complications is paramount. Severe PE is an indication for inducing early delivery, regardless of fetal maturity.

Magnesium sulfate is the most commonly used drug for preventing seizures. Several studies have shown that magnesium sulfate is more effective in preventing seizures than other anticonvulsant drugs and has fewer side-effects. A South African study demonstrated that seizures occurred 10 times less often among pre-eclamptic mothers taking magnesium sulfate compared with those taking no medication. Magnesium sulfate should be administered while giving medications to induce labor, during labor, and up to 24 hours after delivery. Several health organizations (World Health Organization, International Federation of Gynecology and Obstetrics, International Society for the Study of Hypertension in Pregnancy) have all recommended administration of magnesium sulfate to prevent seizures during pregnancy in patients with PE. These organizations do not differentiate between mild or severe cases of PE.

Table 7.4. Medications to control extreme blood pressure in severe pre-eclampsia.

Name	Type	Comments
Sodium nitroprusside	Direct vasodilator	Hypotension possible
Hydralazine	Direct vasodilator	
Labetalol	Alpha/beta blocker	Avoid in asthmatics or patients with congestive heart failure
Nifedipine	Calcium channel blocker	Not approved by FDA (USA) for hypertension

Other forms of hypertension in pregnancy

Pre-existing hypertension or uncomplicated hypertension that develops during gestation is not associated with endothelial dysfunction typical of PE and eclampsia. Pre-existing and gestational hypertension are often treated in the same manner and differentiating between the two forms is difficult. The spontaneous reduction in BP that occurs in the initial stages of pregnancy will often mask mild pre-existing hypertension and lead to a diagnosis of gestational hypertension. One difference between the two forms is that the risk of PE and eclampsia is 2–4 times greater in women with pre-existing hypertension.

Treatment

Treatment of hypertension during pregnancy differs from treating hypertension outside of pregnancy. The goal is to maintain maternal health and protect fetal health. Hypertension in PE occurs abruptly and often becomes severe over only hours or days. Medical treatment of BP ≥160/110 mm Hg in patients with PE decreases the incidence of cardiac and cerebral complications. Most experts agree that therapy should be initiated when the diastolic BP is 100 mmHg or higher. Treatment of gestational and chronic hypertension, which occur over longer periods of time, is recommended for systolic BP ≥150 mmHg and/or diastolic BP ≥100 mmHg, with no evidence of TOD. When TOD is present, antihypertensive therapy is recommended for diastolic BP ≥90 mmHg. Almost all drugs used to treat hypertension can cross the placenta, but despite some research in this area, the full effects of antihypertensive drugs on the fetus are unknown. Therefore, in view of this uncertainty, antihypertensive treatment is, in general, not recommended without other indications. There is little information to suggest one particular class of antihypertensive drug is better than any other (*Table 7.5*).

The following steps should be taken in cases of mild hypertension:

- Monitoring is suggested to be certain that BP does not rise to more severe levels.
- Development of PE (i.e. PE superimposed on pre-existing hypertension) should especially be watched.
- Fetal health must be monitored.
- Moderate sodium consumption (100 mmol/day) is prudent to prevent volume overload.
- Mild, non-intensive exercise should be promoted.
- Without any signs of organ damage, fetal distress, or worsening BP, the baby can be delivered at term.

Methyldopa, a sympathetic blocking drug, appears safe for the fetus. However, methyldopa's antihypertensive effect is mild and may be insufficient to reduce BP to satisfactory levels. The use of CCBs during pregnancy has been increasing, although its use in this setting is controversial.

Table 7.5. Medications that might be used to treat severe pre-existing or gestational hypertension.

Medication class	Comments
Calcium channel blocker	Choice not determined due to unknown safety
Thiazide diuretics	Monitor for volume depletion
Labetalol, alpha/beta blocker	Concerns about the beta-blocker component
Methyldopa	Safe for fetus, but weak activity
Hydralazine	Effective and safe

Thiazide diuretics have been used to control elevated BP during pregnancy, but volume depletion, which leads to decreased circulating blood volume, must be avoided. Beta-blockers are also controversial during pregnancy because of reported complications. The alpha/beta-receptor blocker labetalol is sometimes prescribed. A large-scale meta-analysis suggested that the combined receptor blocker is as safe as any other antihypertensive drug. ACE inhibitors, ARBs, and DRIs are contraindicated.

If medical intervention does not reduce the BP to safer levels, early delivery is required to preserve maternal and fetal health.

CHAPTER 8

HYPERTENSION AND RENAL DISEASE

Overview

BP is closely linked to function and dysfunction of the renal system. Healthy kidneys modulate BP through fluid volume regulation and pressure mechanisms; thus, renal dysfunction is closely linked to elevated BP. The exact association between kidney disease and hypertension, however, is complex, as hypertension can cause kidney damage and, conversely, kidney disease can directly and indirectly cause hypertension. Because hypertension affects a large percentage of the global population, CKD is a major health problem, with approximately 6% of patients with primary hypertension having CKD and at risk of progressing to ESRD. Further compounding the magnitude of the problem, elevated serum creatinine and CKD are associated with increased cardiovascular events and are independent risk factors for cardiovascular mortality.

Hypertension and renal disease

The link between hypertension and AKI and CKD is well-established. Eighty percent of patients with CKD have hypertension, making CKD the most common identifiable cause of hypertension. The prevalence of hypertension is inversely correlated with the GFR, which is a measure of renal function. Hypertension prevalence increases from 65% to 95% of patients as the GFR decreases from 60 ml/minute to 15 ml/minute.

Hypertension is second only to diabetes mellitus as a risk factor for renal dysfunction. The rate at which kidney function declines is variable and is dependent on several factors. Mnay patients with stages 2–4 CKD will progress to ESRD, imposing tremendous personal and economic burdens on families and society, and this burden will only worsen in coming years as the population of individuals with obesity and diabetes mellitus increases. When CKD progresses to ESRD, the only viable treatments are dialysis and renal transplant, which involve huge added expenses to the family and the community.

Therefore, the global costs of caring for patients with CKD, which double in the presence of diseases such as diabetes or cardiovascular disease, is becoming prohibitive.

Hypertension and acute kidney injury

AKI is the sudden loss of renal function leading to reduced urine output and retention of salt and fluid, which can directly cause hypertension. Possible causes of AKI are shown in *Table 8.1*.

The many and differing causes of AKI often make diagnosis difficult. Reduced renal blood flow can occur as a prerenal event, either due to systemic or local causes, including low blood volume (e.g. dehydration or blood loss), reduced CO, renal artery obstruction, and acute intrinsic renal disease. This can lead to 'leaky' filtration altering fluid volume levels. AKI may also occur due to postrenal events, including urinary tract obstruction, such due to a kidney stone or enlarged prostate, which obstruct fluid flow and impede kidney function. AKI requires immediate attention because normal kidney function can often be restored without long-term damage once the underlying cause has been diagnosed and reversed.

Acute glomerular disease

Primary glomerular diseases can cause AKI, with the mechanism of injury often involving the immune system. Immune system-related AKI can be due to antigen–antibody complexes or antibody reactions in the glomerular cells, often involving local or systemic inflammation. AKI can also result from glomerular injury as part of a systemic disease such as diabetes mellitus. Many different mechanisms contribute to glomerular injury (*Table 8.2*). The clinical presentation of each syndrome varies according to the primary disease process.

Decreased renal function is the shared result of all glomerular diseases, and most types reduce renal function by causing hypertension via volume overload from sodium retention. Treatment of short-term glomerular disease consists of sodium restriction and diuretics administration to combat volume overload. After

Table 8.1. Possible causes of acute kidney injury.

- Reduced blood volume
- Low blood pressure
- Heart failure
- Renal artery stenosis
- Glomerulonephritis
- Acute interstitial nephritis
- Renal vein thrombosis
- Kidney stones
- Prostatic hyperplasia
- Kidney trauma

Table 8.2. Glomerular syndromes and their clinical criteria.

Syndrome	Clinical criteria
Rapid progressive	Acute nephritis, acute kidney injury
Glomerulonephritis	Proteinuria
Acute nephrotic syndrome	Edema, hypertension, proteinuria
Chronic renal failure	Decreased glomerular filtration rate, azotemia becoming uremia
Nephrotic syndrome	Proteinuria, hyperlipidemia, lipiduria, hypoalbuminemia
Asymptomatic proteinuria	Subnephrotic proteinuria

glomerular function returns to normal, edema and hypertension usually resolve within days. Proteinuria and hematuria, however, may persist for weeks before resolving.

Acute urinary tract obstruction

Urinary tract obstruction directly interferes with renal function. When left untreated, obstruction may lead to infection, formation of kidney stones, and renal atrophy. Symptoms can range from sharp pain to decreased urinary output. It is possible for urinary tract obstruction to persist undetected for years if only one kidney is involved.

Urinary tract obstruction occasionally lead to mild hypertension. The type of urinary tract obstruction determines how the hypertension is induced. Acute obstruction causes the kidney to compensate by decreasing the GFR and renal blood flow, which activates the RAAS as a response to renal ischemia from reduced blood flow. Bilateral urinary tract obstruction can lead to renal insufficiency or overt renal failure. Elevated BP usually returns to normal when the obstruction is removed.

Hypertension and chronic renal dysfunction

CKD is the gradual reduction in kidney function over time. In contrast to AKI, the initial stages of CKD are usually symptom-free, and often patients are unaware of their condition until they have lost significant renal function. A variety of factors may lead to CKD including age, genetic predisposition, and injury (and a combination of these factors). Hypertension or diabetes, alone or in combination, are often associated with CKD. Treatment usually consists of measures to stop

or slow loss of renal function and treatment of the contributing underlying process(es). CKD often leads to ESRD, a stage for which the only remaining solution is renal replacement therapy with either long-term dialysis or kidney transplantation.

Chronic kidney disease

CKD is defined by the National Kidney Foundation – Kidney Disease: Outcome Quality Initiative (NKF-K/DOQI) using two different parameters. (1) 'Structural or functional abnormalities of the kidney, with or without decreased GFR, manifest by either pathological abnormalities or markers of kidney damage'. These abnormalities can be detected by histology or imaging studies, and common markers include proteinuria and albuminuria. (2) GFR when it is 'less than 60 ml/minute/1.73 m² with or without kidney damage'. Both definitions require persistence of renal dysfunction for at least three months or longer.

CKD can be classified into five stages based on GFR. Stage 1 is GFR of 90 ml/minute/1.73 m² with some albuminuria; stage 2 is GFR of 60–90 ml/minute/1.73m²; stage 3 is GFR of 30–60 ml/minute/1.73 m²; stage 4 is GFR of 15–30 ml/minute/1.73m²; and stage 5 is GFR of less than 15 ml/minute/1.73 m².

What is the mechanistic link between reduced renal function and hypertension? Many of the earlier chapters detailed how the kidneys directly control fluid volume and utilize signaling pathways to cause vasoconstriction, thereby altering CO and SVR. Poorly functioning kidney therefore directly cause sodium and fluid retention, and renal insufficiency eventually leads to elevated BP and subsequent sustained hypertension. Hypertension can then cause renal damage, leading to further declines in renal function. Much of the injury to the kidney because of hypertension probably occurs because of glomerular hypertension (Figure 8.1).

Glomerular hypertension occurs with increased glomerular capillary flow rate and/or increased glomerular intracapillary hydraulic pressure. Autoregulatory systems modulate kidney function. For example, arteriolar constriction shields veins and capillaries from high BP. Glomerular hypertension occurs due to rapid

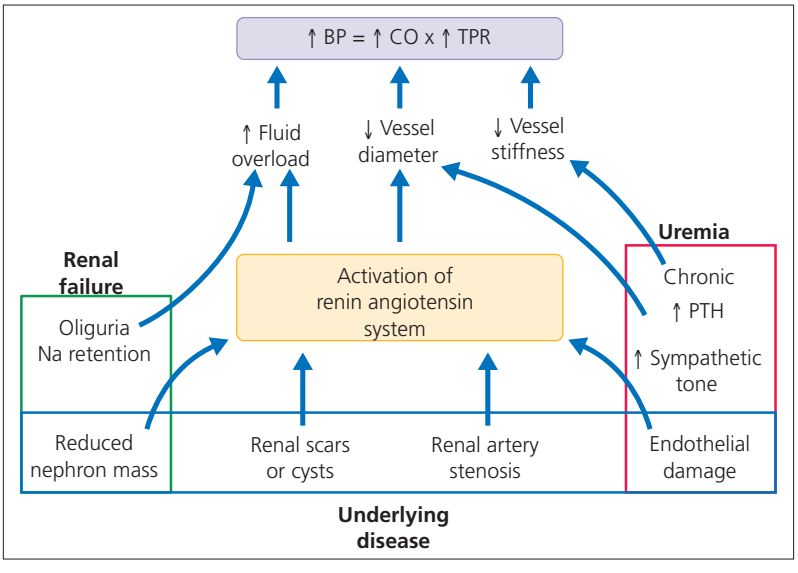


Fig. 8.1 Interplay of different factors in the generation of hypertension in chronic kidney disease. BP, blood pressure; CO, cardiac output; TPR, total peripheral resistance; PTH, parathyroid hormone; Na, sodium. (Adapted from Hadtstein C, Schaefer F (2008) Hypertension in children with chronic kidney disease: pathophysiology and management. *Pediatr Nephrol* **23:**363–371.)

BP elevation, which overwhelms normal regulatory systems. The result is increased intracapillary BP, which damages glomerular cells and decreases renal function, causing volume overload and a further rise in BP.

There are many factors that can contribute to increased BP-related renal damage. These factors include: (1) sodium balance; (2) increased SNS activity, which signals adrenergic receptors and causes BP rise (physiological stress is the common cause of increased SNS signaling); (3) RAAS activation; (4) increased insulin resistance due to obesity or diabetes mellitus; and (5) hormone signaling, caused by pregnancy and endocrine disorders.

Current evidence supports aggressive BP control in patients with diabetes mellitus and CKD, and recent hypertension guidelines recommend a target BP of less than 130/80 mmHg for high-risk patients. Some studies suggest that even lower BP goals may result in even greater renal and retinal protection and stroke reduction in type-2 diabetes mellitus. Current guidelines place particular emphasis on the importance of optimal BP control to preserve cardiovascular and renal function.

Diabetic nephropathy

Diabetes mellitus causes many long-term changes that negatively impact renal function and BP control. Much of the morbidity and mortality associated with diabetes mellitus is due to complications from macrovascular and microvascular disease. The most important macrovascular disease is atherosclerosis. Microvascular abnormalities include microangiopathy, retinopathy, nephropathy, and neuropathy. If CKD is left untreated, may progress to ESRD. DN is the leading cause of ESRD in the USA and Europe.

The mechanisms of DN are not fully understood, but a number of hemodynamic and metabolite changes are known to be involved. Elevated levels of blood glucose contribute to renal injury. Decreasing blood glucose levels through diet modification or drug treatment results in decreased albuminuria. Signaling molecules such as cytokines are important in initiation and progression of the disease. Transforming growth factor-beta is one of the main growth factors involved. Glomerular hypertension is also a contributory factor, as it causes a worsening of hypertension, which is slowed by antihypertensive treatment.

Intercapillary glomerulosclerosis and diffuse glomerulosclerosis are the two main components of DN. Damage imposed by these two disease processes leads to increased proteinuria as glomerular filtration breaks down. Proteinuria is usually the first sign of nephropathy and is associated with a three-fold higher risk of mortality due to CVD. The other major measurable defect is reduced GFR, which continues to decline until ESRD is reached. These changes in renal function result in sodium and fluid retention and volume overload, which are major contributors to hypertension associated with DN.

Combined RAAS blockade with ACE inhibitors and ARBs reduces BP and proteinuria when administered at higher doses in patients with type-1 and type-2 diabetes. The COOPERATE Trial in people with non-diabetic nephropathy showed a superiority of combined RAAS blockade after three years of therapy over single-site blockade. Although BP reduction was equivalent between the two groups, the antiproteinuric effect of the combination was superior to either ACEs or ARBs when used alone.

End-stage renal disease

The combination of long-term hypertension, diabetes mellitus, CKD, and other factors often leads to ESRD. The only treatment available for ESRD is dialysis to regulate fluid volume. Current advanced dialysis technology allows patients to live for many years without functioning kidneys. Kidney transplantation is the only cure for ESRD and restoration of renal function.

Hypertension is common in ESRD, with over 80% of patients hypertensive at the start of treatment for ESRD. Renal function is greatly compromised in ESRD, with significant sodium and water retention. Excess fluid volume causes increased BP by increasing CO and triggering autoregulation systems that increase SVR. Dialysis for ESRD reduces BP, with only one-half of patients on hemodialysis remaining hypertensive, and one-third of those undergoing peritoneal dialysis. Part of this improvement in BP is due to improvements in volume control during dialysis. However, many dialysis patients remain hypertensive even with aggressive medical therapy.

Hypertension is the leading predictor of coronary artery disease in uremic patients. The lack of a significant correlation between high BP and cardiovascular events in hemodialysis patients may be due to poor ventricular function, leading to low BP in some patients with increased cardiovascular mortality. A U-shaped relationship between BP and mortality is present, with high mortality risk at the lowest and highest levels of BP. The etiology of hypertension in dialysis patients is multifactorial and includes volume excess, activation of the RAAS, increased sympathetic activity, increased endothelial-derived vasoconstrictors, administration of erythropoietin, and arterial calcification. Optimal BP control in dialysis patients is controversial. Systolic BP over 180 mmHg is associated with poor outcomes in several studies. Most data support the use of predialysis BP measurement to guide therapy, as this BP is often thought to be the highest pressure, although this is not conclusive in published literature. Tight BP control in dialysis patients may lead to symptomatic hypotension after dialysis, especially in the presence of large interdialytic weight gain. It is reasonable to keep the systolic BP below 160 mmHg and diastolic BP below 90 mmHg before dialysis. Studies of ABPM in hemodialysis patients have shown that BP decreased during the first night, but not the second night, after dialysis. The absence of nocturnal dipping of BP has been correlated to the severity of cardiovascular TOD. Treatment of hypertension in dialysis patients includes control of volume status, prolonged or more frequent hemodialysis, and the use of appropriate antihypertensive medications.

The other option for correcting ESRD is kidney transplantation, and hypertension is one of the major complications of kidney transplantion. If hypertension is not adequately controlled, high BP may cause transplant dysfunction. Immunosuppressive therapy can lead to nephrotoxicity and continued hypertension. Renal artery stenosis occurs in about 4% of kidney transplant patients with hypertension, which can lead to RVHT or renal ischemia. Another concern in transplant patients is teh possibility is that the remaining kidney may contribute to hypertension.

Hypertension and kidney transplant recipients

Hypertension in renal transplant recipients is defined as BP greater than 140/90 mmHg. Prior to introduction of cyclosporine, post-transplant hypertension was seen in less than 50% of all patients. Since the introduction of calcineurin inhibitors, hypertension occurs more frequently, ranging from 70% to 90% of kidney transplant recipients. The incidence of steroid-induced hypertension has been estimated at 15%. It is well known that hypertension is a major cardiovascular risk factor and is associated with reduced patient and graft survival. Regression analysis has demonstrated that increased BP is an independent risk factor for kidney graft failure.

CCBs and ACE inhibitors are similarly effective in reducing BP in renal transplant recipients. In a randomized double-blind study comparing nifedipine and lisinopril with the end-point of allograft function during two years of therapy, nifedipine was associated with better renal function and was superior to lisinopril in the treatment of post-transplant hypertension. Therapy with beta-blockers has been shown to reduce morbidity and mortality after MI and is beneficial in patients with CHF. The National Kidney Foundation task force for cardiovascular disease recommended that the goal of therapy should be to reduce BP to below 135/85 mmHg for renal patients without proteinuria and below 125/75 mmHg for patients with proteinuria, but these may be unachievable goals based on recent studies.

Treatment of hypertension in patients with renal disease

Control of hypertension is critical in preventing complications of renal dysfunction. Persistent renal dysfunction will only lead to more difficulties in controlling BP.

Goals of treatment

Management of hypertension varies according to the nature of the renal disease (*Table 8.3*). Many types of acute renal hypertension can be corrected by treating the direct cause of renal failure. Chronic and resistant hypertension may also be corrected if they are secondary to other treatable causes. The next concern is preventing or slowing further deterioration of renal function. Worsening renal function makes hypertension more difficult to control. Even mild hypertension should be treated to prevent further kidney damage.

Table 8.3. Goals of hypertension treatment in patients with complications of kidney disease.

- Identify and treat reversible causes
- Slow progression of renal dysfunction
- Treat complications
- Proactive treatment of end-stage renal disease

The target BP for CKD patients is less than 135/85 mmHg. Patients with CKD who can lower their diastolic BP below 90 mmHg can preserve GFR better than patients who remain hypertensive. Unfortunately, target BP levels can be difficult to achieve. Only 37% of patients in one study were able to reduce their BP to the recommended level. Many CKD patients must take a combination of complex medications to control hypertension, which usually includes a diuretic and a RAAS blocker (Figure 8.2, *Table 8.4*).

Sodium intake is particularly important in hypertensive patients with renal dysfunction. The recommended daily sodium intake is 44–88 mEq. Sodium restriction helps control fluid volume improve the efficacy of antihypertensive medications.

Rational selection of antihypertensive drugs

RAAS inhibitors are particularly important treatment strategies for patients with CKD and ESRD. There is also evidence that ACE inhibitors provide an additional level of renal protection beyond their effect on systemic BP. Several clinical trials have supported the use of ACE inhibitors in CKD patients with hypertension by showing that treatment with ACE inhibitors or ARBs slows the rate of renal disease progression. ACE inhibitors can reduce the amount of proteinuria by up to 45% in some patients. ARBs have comparable effects.

ACE inhibitors provide better reduction of glomerular pressure and renal function preservation than other types of antihypertensive medications. Other classes of antihypertensive drugs do not improve proteinuria, suggesting that the effect of RAAS inhibitors is additive to their BP lowering effects. ACE inhibitors cause a greater efferent vasodilation of the arteriolar vessels by blocking intrarenal AT II. The effect of vasodilation on the efferent vessel is greater than the decrease in the afferent resistance. This lowers the glomerular pressure and helps to prevent further glomerular sclerosis. This protective effect on renal function by ACE inhibitors has been best demonstrated in the Ramipril Efficacy in Nephrology Study, in which ramipril was shown to be renoprotective. Protection from proteinuria correlated with slowing the progression of kidney disease.

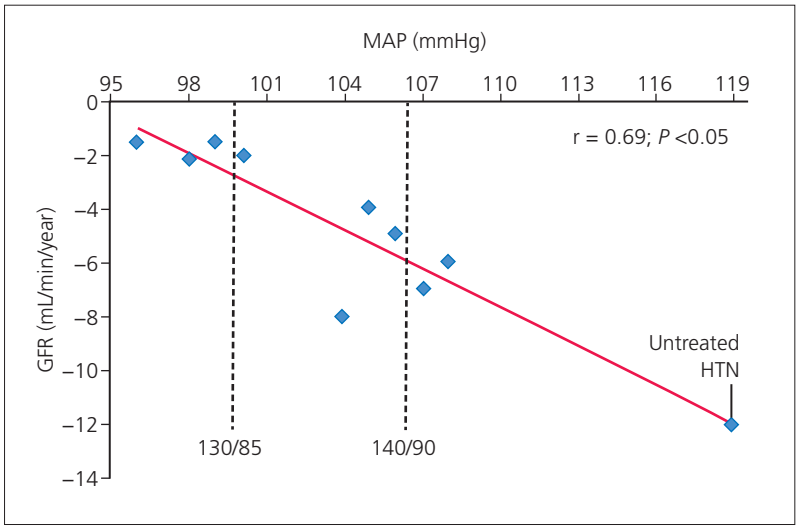


Fig. 8.2 Relationship between the achieved blood pressure control and declines in glomerular filtration rate in six clinical trials of diabetic renal disease and three of non-diabetic renal disease. HTN, hypertension; MAP, mean arterial pressure. (Adapted from Bakris GL, Williams M, Dworkin L *et al*. (2000) Preserving renal function in adults with hypertension and diabetes. A consensus approach. *Am J Kid Dis* **36:**646–661.)

Table 8.4. Blood pressure goals, non-pharmalogical therapy, and pharmalogical therapy recommended by the National Kidney Foundation Task Force on Cardiovascular Disease in Chronic Renal Disease.

Population	Blood pressure goal (mmHg)	Non-pharmacological therapy	Pharmacological therapy
General population	<140/190	Reduction in dietary salt, exercise	Beta-blockers, diuretics
CKD stages 1–4 with proteinuria (>1 g/day) or diabetic kidney disease	<125/75	Reduction in dietary salt	ACE inhibitors or ARBs (with or without the additon of a diuretic), or CCBs in kidney transplant recipients
CKD stages 1–4 without proteinuria (<1 g/day)	<135/85	Reduction in dietary salt	ACE inhibitors or ARBs (with or without the addition of a diuretic), or CCBs in kidney transplant recipients
CKD stage 5	<140/90	Reduction in dietary salt; reduction in fluid intake and ultrafiltration in dialysis patients	Any, except diuretics in dialysis patients

CKD, chronic kidney disease; ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; CCBs, calcium channel blockers. (From National Kidney Foundation (NKF) Kidney Disease: Outcomes Quality Initiative (K/DOQI) Advisory Board (2002) K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kid Dis* **39(2 Suppl 2):**S1–246, with permission.)

Diuretics are also useful and often necessary for hypertension management in patients with renal disease, because volume excess is a common problem in CKD and ESRD. Loop diuretics are most often used for patients with advanced renal disease rather than thiazide diuretics. Most thiazide and loop diuretics act on the luminal side of the tubular membrane. Acidic or basic secretory pathways are utilized so the diuretics can cross the membrane. However, in CKD, blood flow is often reduced, resulting in a build-up of organic acids in the kidneys. These organic acids directly compete with acidic diuretics at the site of action. Another approach is use of more powerful drugs at normal doses. Generally, loop diuretics are more potent diuretics and can partially overcome the lower effective dose.

CCBs can also be useful for treating hypertension, but glomerular hypertension is a possible concern because this will cause afferent arterioles to dilate more than

efferent arterioles. This can increase glomerular pressure and lead to further renal damage. However, if CCBs lower the systemic BP enough, glomerular pressure will decrease. Although non-DHP CCBs decrease the level of proteinuria, DHP CCBs do not have this effect. The Ramipril Efficacy in Nephrology Study supports this result. DHP CCBs do not appear to have any renal protective effect and this class of drug is most likely a second- or third-line medication for treatment of hypertension in patients with proteinuria and renal damage.

Specific concerns

When treating hypertension in patients with AKI, the most important step is to determine the underlying cause of renal disease. Usually, elevated BP will normalize if the underlying condition is corrected. Differing etiologies of AKI can make this difficult. If hypertension must be treated, approaches differ depending on clinical manifestations. Signs of fluid retention, such as edema, can be controlled with diuretics or even dialysis. In other types of AKI, hypertension may be better treated using an RAAS antagonist. Hypertension associated with scleroderma and vasculitis should be treated with an ACE inhibitor.

Treatment of hypertension in diabetic patients is more involved and challenging. In addition to lowering BP, other complications of diabetes must also be dealt with. Progression of DN is influenced by blood glucose levels, and reducing hyperglycemia slows the progression of neuropathy, according to the findings of the Diabetic Control and Complications Trial Research Group Study. Reducing DN progression can also help prevent worsening hypertension.

Decreasing the BP of diabetic patients also slows progression of DN, again demonstrating a link between BP and renal function (and dysfunction). Target levels for BP are 135/85 mmHg, or lower for hypertensive patients with CKD, which can be accomplished with lifestyle modifications and medical treatment. ACE inhibitors or ARBs are usually the first choice because of their antihypertensive action and renal protection. Combination treatment with multiple drugs is usually needed to control BP, particularly diuretics.

Hypertension is especially problematic in patients on dialysis because of the difficulty in controlling extracellular volumes. One approach is to increase the use of hemodialysis. Daily hemodialysis results in better control of BP because the differences between high and low volume are minimized. Hemodialysis provides better BP control than peritoneal dialysis.

CHAPTER 9

RENOVASCULAR HYPERTENSION

Overview

RVHT is a form of secondary hypertension resulting from activation of pressor mechanisms due to renal ischemia. Although RVHT is caused by critical stenosis of the renal artery, the presence of renal arterial disease is not synonymous with RVHT. It is possible to detect renal artery stenosis in normotensive people where hypofusion from the stenosis is not severe. Although RVHT is an uncommon cause of hypertension in the general population, it is important that it is identified, as this cause of hypertension can be cured in some instances.

Most estimates attribute less than 1% of cases of mild hypertension to renovascular disease. Among patients with resistant, acute onset, and severe forms of hypertension, the prevalence of renovascular disease is higher. As many as one-third of patients with accelerated and malignant hypertension may have RVHT.

Possible causes of renovascular disease

Stenosis of the renal arteries is the most common form of renovascular disease that can result in hypertension. Narrowing of the arteries may occur in one kidney (unilateral) or both kidneys (bilateral). Bilateral renal artery stenosis is more likely to cause renal failure than unilateral stenosis. Atherosclerosis is the cause of the majority of cases of renal artery stenosis, but there are many other types of intrinsic and extrinsic lesions that may occur and that obstruct renal blood flow. Fibromuscular dysplasia, arterial dissection, arteritis, and injuries to the renal artery are some examples.

Over 80% of renal artery stenosis cases are due to atherosclerosis. Narrowing of the artery is due to the formation of plaque, which is composed mostly of cholesterol and cellular debris. Inflammation and disorders of coagulation may contribute to initiation and progression of renovascular disease. Often, endothelial dysfunction will activates the inflammatory response and coagulation abnormalities, which trigger vascular disease and plaque formation. High BP, tobacco use, diabetes mellitus, and advanced age are all likely to contribute to increased endothelial cell stress. Atherosclerotic lesions are often progressive.

Mechanisms leading to hypertension

Renal artery stenosis causes several hemodynamic and hormonal changes that can lead to RVHT. Some studies have estimated that narrowing must exceed 80% of the intra-arterial lumen before blood flow is restricted enough to cause hypofusion and activation of RAAS ischemia (Figure 9.1). The juxtaglomerular apparatus senses reductions in arterial blood flow and triggers the RAAS in a similar way to normal physiological responses to low blood volume and low BP. Renin release leads to increased levels of AT II, causing arterial vasoconstriction (Figure 9.2). Increased AT II stimulates aldosterone secretion, which causes sodium and water retention and changes in SVR and CO, leading to increased BP. In cases of long-term renovascular disease, hypertension may persist after corrective removal of the stenosis because of autoregulatory control mechanisms.

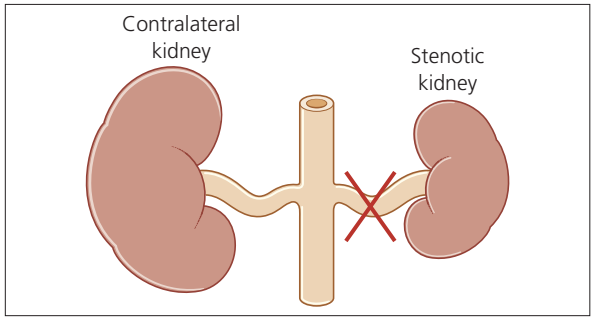


Fig. 9.1 Schematic representation of renovascular hypertension.

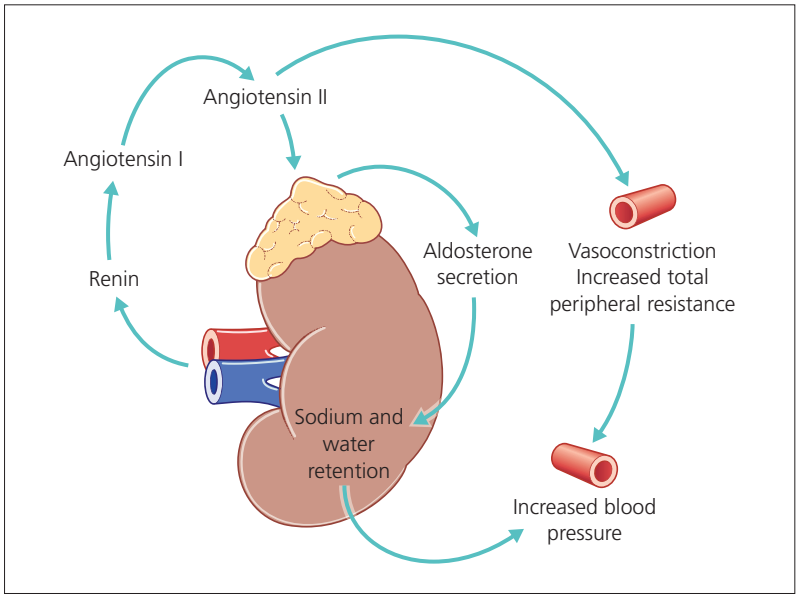


Fig. 9.2 Schematic representation of angiotensin conversion.

Clinical findings

There are many clinical scenarios suggesting that renovascular disease might be responsible for systemic hypertension (*Table 9.1*). These include: a sudden rise in BP in a person with existing hypertension, particularly older patients; difficult BP control with a long prior history of successful treatment; rapid decline in renal function; significant hypertension in young people should also be investigated for possible RVHT; absence of other risk factors and a negative family history; and resistant hypertension. A good rule is that any unexplained change in BP or typical onset of hypertension is a reason to suspect RVHT.

Some patients with critical bilateral renal artery stenosis or renal artery stenosis in a solitary kidney may present with recurrent 'flash' pulmonary edema. This entity is known as 'Pickering syndrome' and is one of the few clear indications for endovascular procedures in atherosclerotic renovascular disease.

Diagnostic tests and screening

Screening for renovascular causes of hypertension is not recommended in the routine evaluation of hypertensive patients because of the (relative) rarity of RVHT in usual practice settings. However, when patients present with clinical manifestations suggestive of RVHT, further diagnostic evaluation is indicated, following careful consideration.

Table 9.1. Clinical indicators of possible renovascular hypertension.

- No history of familial hypertension
- Resistant hypertension
- Severe hypertension
- Abrupt-onset hypertension
- Dyslipidemia
- Decreased renal function
- Smoking
- Early-onset hypertension (<30 years old)
- Kidney size difference
- Secondary aldosteronism
- Recurrent flash pulmonary edema

There is no single sensitive, specific, and inexpensive test to diagnose renal artery stenosis. Renal arteriography (Figures 9.3 and 9.4) remains the gold standard against which all diagnostic tests are compared, but it is an invasive procedure and is not recommended without strong suspicion of RVHT. Several screening tests are available, both invasive and non-invasive, utilizing a number of different techniques (*Table 9.2*).

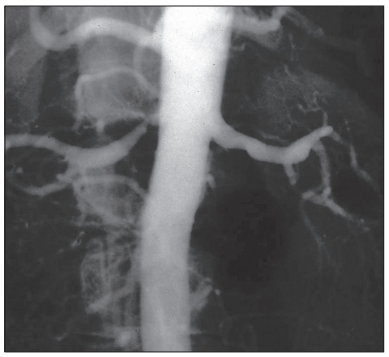


Fig. 9.3 Arteriographic view of bilateral artherosclerotic renal artery stenosis.

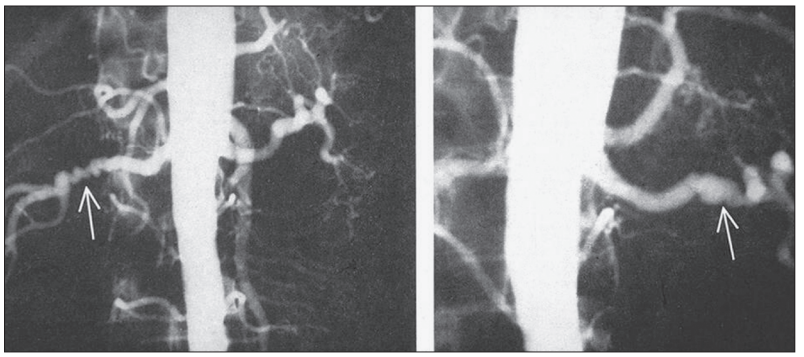


Fig. 9.4 Arteriographic views of fibromuscular dysplasia of renal arteries (arrows).

Table 9.2. Diagnostic methods used to diagnose renal artery stenosis, with advantages and disadvantages specific to each assay.

Assay	Advantages	Disadvantages
Plasma renin activity (with prior administration of captopril)	Easy to test	High false-positive rate; variable
Renal vein renin	Few	Requires catheter; cannot screen
MRI angiography	Non-nephrotoxic contrast agent	Expensive equipment
Spiral CT angiography	Less invasive; 3-D images	Possibly nephrotoxic
Color Doppler ultrasound	Non-invasive; flow rates; cheaper	Requires expertise
Renal arteriography	High diagnostic power; 'gold standard'	Invasive

Scintigraphy

Renal scintigraphy is most useful following prior administration of the ACE inhibitor captopril (Figure 9.5) because kidneys with renal artery stenosis show declines in GFR after administration of an ACE inhibitor. This phenomenon was first detected in bilateral renal artery stenosis because of a systemic decrease in GFR. In cases of unilateral RVHT, captopril induces significant changes in the time–activity curves of affected kidneys. Often, the other kidney, if unaffected, increases its GFR because autoregulation of GFR is disrupted by reduced levels of AT II in the presence of ACE inhibition. Such changes in GFR are not observed in patients with insignificant renal artery stenosis or with normal renal arteries. Time-lapse renography and scintigraphy measurements can detect changes in the kidneys and global decreases in GFR. Therefore, captopril greatly increases the sensitivity of renography for detecting renal artery stenosis. However, captopril-enhanced renography does have limitations. The test should not be performed in patients taking ACE inhibitors. Patients on ACE inhibitors must discontinue their medication for a period of time prior to the test. AKI may occur in patients with bilateral renal artery stenosis. In unselected patient populations, captopril scintigraphy has lower sensitivity than in high-risk populations, which limits its value as a screening test. Predictive values of the test are approximately 90%, an improvement over regular renography. In summary, although captopril-enhanced renography is useful in selected cases, and distinctly superior to plain scintigraphy, it is not a dependable for screening.

Plasma renin activity

PRA is elevated in some patients with RVHT and can be used as screening method for diagnosing RVHT. PRA levels are affected by many variables, making this test dificult to interpret in normal clinical settings. For example, renin secretion changes throughout the day and renin levels are influenced by diet (sodium

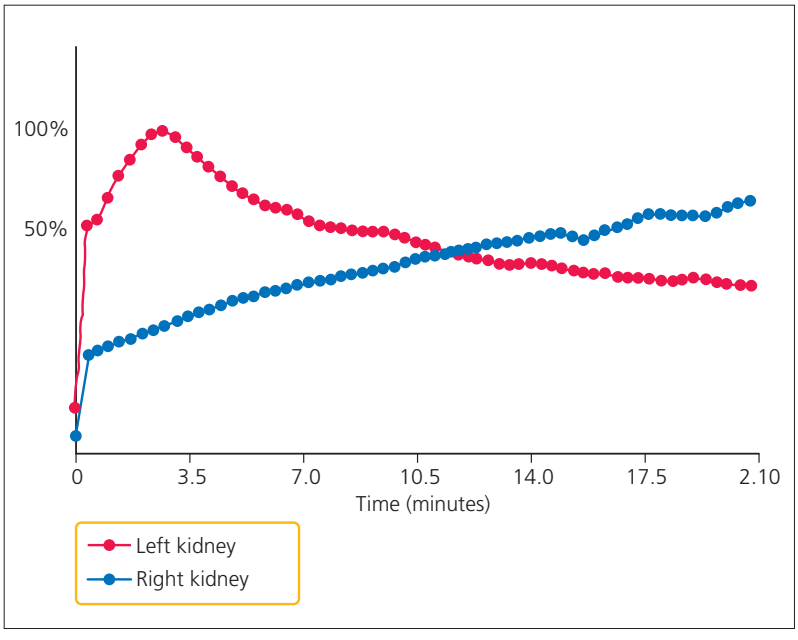


Fig. 9.5 Abnormal captopril-enhanced renal flow scan (renal artery stenotic, right kidney).

intake), age, sex, and race. Only 50–80% of RVHT patients have increased levels of PRA. Therefore, PRA measurements have low specificity and sensitivity in the diagnosis of RVHT, and renin profiling alone has little role in evaluating patients with possible RVHT.

As with renography, ACE inhibitors have been shown to enhance the sensitivity of PRA in the diagnosis of RVHT. ACE inhibition causes renin levels to increase due to reduced AT II. This test requires at least some kidney function and is not useful in the presence of bilateral renal artery stenosis or renal insufficiency. Patients must discontinue ACE inhibitor drugs prior to the test. This test has only, at best, 75% sensitivity for detetcing RVHT, and false-positive results are common. In summary, complexities in test performance an low sensitivity limit the usefulness of PRA measurements in the diagnosis of renal artery stenosis.

Angiography

Two methods of angiography, magnetic resonance angiography (MRA) and spiral computed tomography angiography (CTA), are useful for diagnosing renal artery stenosis. Both methods have greater sensitivity and accuracy and are less invasive than renal arteriography.

Magnetic resonance angiography

MRA is based on the same technologies used in MR imaging to provide details about blood vessels, including renal vessels (Figure 9.6). Some studies report a sensitivity of 100% for detection of renal artery stenosis, although other studies have reported lower sensitivity.

There are several advantages of MRA in addition to its high sensitivity. GFR, renal size, and renal blood flow can be evaluated simultaneously, providing more information about renal function. MRA is a non-invasive procedure that does not require radioactive contrast media. (The use of gadolinium-enhanced MRA has nearly vanished due to its adverse effects.) However, MRA has certain disadvantages. It is an expensive technique and cannot be used in patients with metallic implants such as pacemakers. The design of current machines makes it difficult to image very large patients or patients who are claustrophobic.

In summary, despite certain drawbacks, MRA is a highly useful technique in screening for renal artery stenosis.

Computed tomography angiography

Spiral (helical) CTA is an emerging technique that is also highly accurate in screening for renal artery stenosis (Figure 9.7). CTA requires intravenous administration of a contrast agent. The diagnostic accuracy of CTA is excellent, with up to 98% sensitivity and 94% specificity. Spiral CTA also visualizes the arterial lumen and arterial walls in three-dimensional space, thus providing a very accurate view of the renal arteries, which is useful for planning angioplasty procedures. Distal and accessory vessels can also be visualized.

CTA does have limitations, including its use of radioactive contrast agents, which may cause nephrotoxicity. This prevents its use in patients with reduced renal function. With CTA it is also difficult to differentiate between complete occlusion and just severe stenosis. Further experience is required to assign a definitive role for this technique in the evaluation of patients suspected of having renal artery stenosis.

Ultrasound

Renal artery duplex ultrasound combines standard ultrasound technology for static images of organs and vasculature with Doppler technology for information about dynamics. When Doppler data are presented as graphs, the test is duplex Doppler ultrasound. When velocity data is converted and overlaid as a color image, it is presented in a form termed color Doppler ultrasound.

Duplex Doppler scanning is non-invasive and thereare no limitations in patients with renal insufficiency or bilateral renal artery stenosis. The original duplex Doppler technique was challenging and required experienced operators for clinical use and, as a result, the test had a higher frequency of inaccurate or difficult-to-interpret information, with false-negative results as high as 20%. However, color Doppler ultrasound and other advances have now made this a reliable tool for the diagnosis of renal artery stenosis. Sensitivity and specificity are as high as 98%, comparable with renal arteriography. In summary, ultrasound, when conducted by experienced operators, is a highly accurate and safe procedure in initial screening for renal artery stenosis.

Renal arteriography

Renal arteriography is the most accurate means of diagnosing renal artery stenosis, and it has the added benefit of immediate angioplasty if a stenosis is found. This test uses catheter-based injection of contrast agent to assist in radiographic-based visualization of the renal vessels, and it is relatively fast.

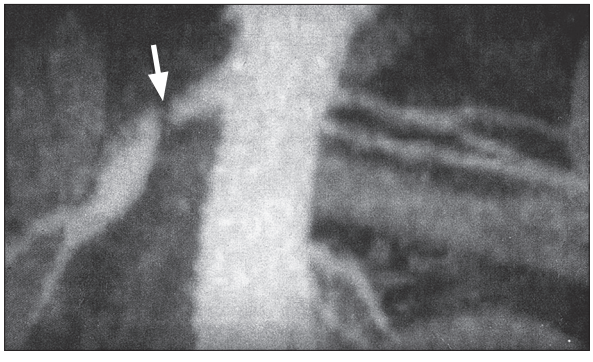


Fig. 9.6 Magnetic resonance angiogram showing renal artery stenosis (arrow).

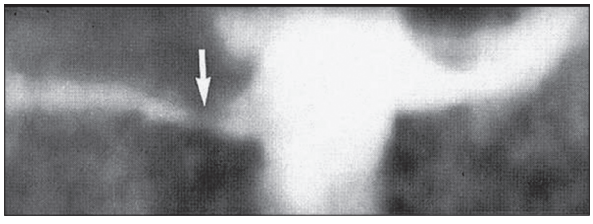


Fig. 9.7 Computed tomography angiogram showing renal artery stenosis (arrow).

Renal arteriography has several limitations. It cannot provide much information about the feasibility of correction of stenoses or quantify the degree of vascular occlusion. It is an invasive procedure, associated with many complications such as bleeding, bruising, and infection. The catheter may damage vessels walls, including possible dissection, which can be fatal. Also, the contrast agent may cause complications. Although renal arteriography is an excellent test, clinicians must weigh its risks against its diagnostic power.

Current recommendations

Not all patients with hypertension should be screened for renovascular disease. There should be clinical indications suggestive of RVHT before testing. While renal arteriography is the most accurate test, it is also the most invasive. In patients with low probability of RVHT, less invasive techniques are a better option for screening. Various groups have provided recommendations for screening

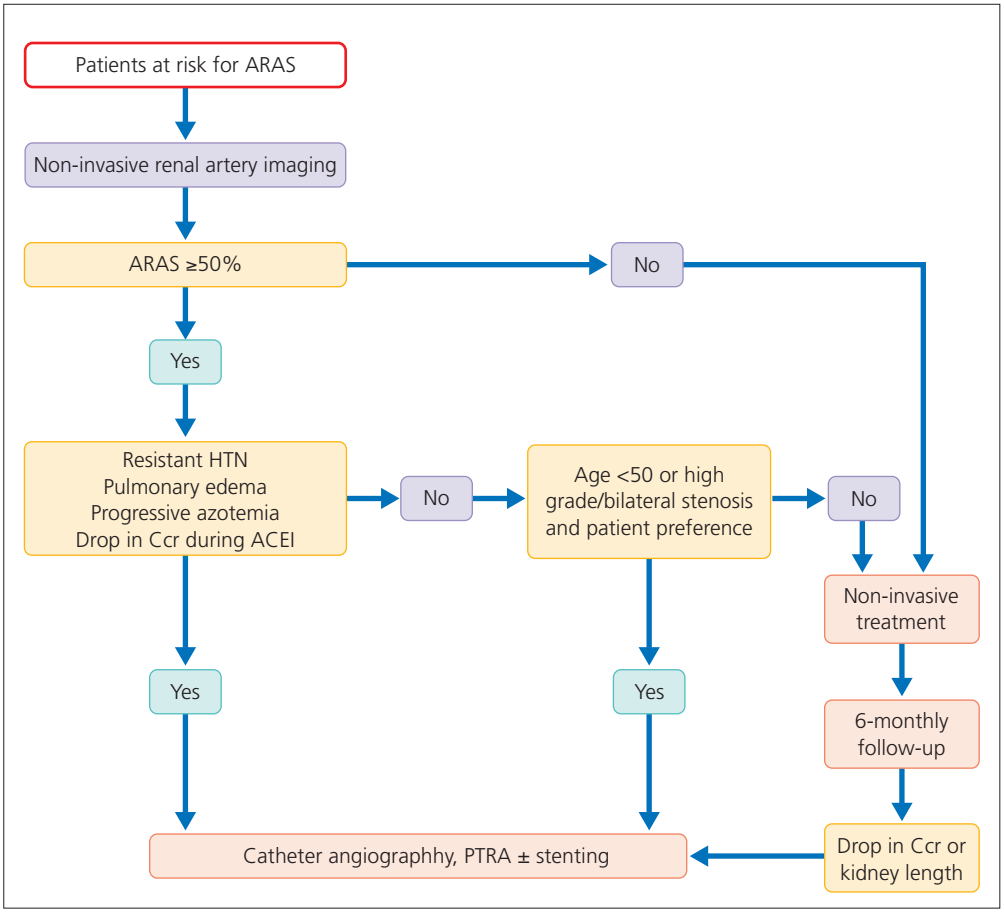


Fig. 9.8 Suggested evaluation and treatment for patients with suspected atherosclerotic renal artery stenosis (ARAS). HTN, hypertension; PTRA, percutaneous transluminal renal artery angioplasty; Ccr, creatinine clearance. (Adapted from Plouin P-F, Rossignol P, Bobrie G (2001) Atherosclerotic renal artery stenosis: to treat conservatively, to dilate, to stent, or to operate? *J Am Soc Nephrol* **12:** 2190–2196.)

techniques based on the estimated risk for renal artery stenosis, although there is no universal agreed-upon strategy that applies to all patients. Testing should only be performed if there is some likelihood of surgical intervention in addition to medical treatment.

Patients at risk for atherosclerotic renal artery stenosis (ARAS) (Figure 9.8) are those with abrupt-onset or resistant hypertension, hypertension with abdominal bruits or atherosclerotic disease elsewhere, recurrent pulmonary edema, or azotemia with ACE inhibitor treatment. Non-invasive renal artery imaging may use duplex Doppler ultrasonography, MRA, helical CTA, or intravenous digitized subtraction angiography.

Management of renovascular hypertension

RVHT is a rare form of secondary hypertension and, as with many other types of secondary hypertension, correcting the underlying condition may eliminate or improve hypertension. Treatment options are medical angioplasty or surgical repair (*Table 9.3*). Recently, the American College of Cardiology and the American Heart Association published guidelines on the treatment of RVHT. These guidelines recommend medical treatment to control hypertension for patients with unilateral renal artery stenosis. Patients who do not respond to treatment or have a more severe type of hypertension (e.g. resistant, malignant) should have revascularization. Surgery is recommended only for complex stenoses. A recent meta-analysis found less evidence to support specific recommendations.

Medical treatment

Hypertension secondary to renovascular disease is due to ischemia. The most effective drugs for treatment of RVHT are RAAS inhibitors; other antihypertensive drugs are less effective. A study of several hundred patients demonstrated that an ACE inhibitor was effective for controlling BP in 80% of patients over a period of several months. ARBs have also been used successfully to treat hypertension associated with renovascular disease. However, combinations are often necessary to achieve therapeutic goals.

Table 9.3. Treatment for renovascular hypertension.

Treatment	Advantages	Disadvantages
Medical	Non-invasive; improves BP	May not change stenosis; atrophy of the kidneys
Angioplasty (stent)	Can reduce stenosis; improves BP	Invasive; requires catheter; restenosis
Surgery	High success rate; restenosis; low chance of major complications	Morbidity

All combinations should include a RAAS inhibitor, except in patients for whom RAAS agents are contraindicated. BP should be aggressively managed and followed with clinical evaluations as well as monitoring of renal function, and, if indicated, renal size.

Angioplasty (and stent placement)

Angioplasty (with a stent) can be performed to facilitate reperfusion of ischemic kidneys. In cases of severe or resistant hypertension and progressive renal insufficiency, it may be prudent to consider angioplasty as soon as possible. Angioplasty has an approximately 70% success rate, defined as an improvement or stabilization of blood flow compared with levels prior to performing the procedure. About 25% of patients who undergo angioplasty have restenoses within one year of the procedure. Obstruction due to fibromuscular dysplasia lesions are more amenable to angioplasty than atherosclerotic lesions.

One method of improving the efficacy of angioplasty procedures in atherosclerotic disease is stent implantation, which has used successfully in both bilateral and unilateral renovascular disease. A recent two-year follow-up study reported that restenoses occur less often (17% restenosis rate) with stent placement compared with angioplasty without stent placement (26% restenosis rate). Over two-thirds of patients who received stents during their angioplasty procedure had improvement in hypertension levels.

Surgical treatment

Surgery, although performed less often than prior to the introduction of angioplasty, is an effective treatment for RVHT, especially in patients who have severe renal artery stenosis due to atherosclerosis, with technical success in as many 90% of procedures. Success is greatest in patients in whom hypertension has been present for less than five years. Surgery may improve kidney function in patients with renal impairment. In addition to improved hypertension, renal function may also improve after suregry. Surgery most often involves arterial bypass of the stenosis. Aortorenal bypass techniques are the most often employed. Other types of bypass, including hepatorenal, splenorenal, or ileorenal, are used when manipulation of the aorta is contraindicated.

A major concern with surgical procedure is patient morbidity or mortality. Coronary artery disease, cerebrovascular disease, and peripheral vascular arterial disease are common comorbidities in patients with atherosclerotic renal artery stenosis. Renal insufficiency adds to the surgical risk for all patients.

CHAPTER 10

10

PRIMARY ALDOSTERONISM

Overview

Primary aldosteronism (PA, also called hyperaldosteronism) comprises several syndromes with similar manifestations, including elevated BP, hypokalemia, increased aldosterone, and reduced renin plasma levels. In the past, PA was thought to be an uncommon cause of secondary hypertension, occurring in approximately 1% of all patients. However, changes in diagnostic methods have raised the estimates of hypertension attributable to PA, some studies estimating the prevalence at up to 10–15% of secondary hypertension cases. The specific treatment strategy depends on which subtype is causing the PA (*Table 10.1*), but in some cases PA-related hypertension can be improved and even cured with treatment of the underlying disorder.

Table 10.1. Causes of primary aldosteronism.

- **Unilateral aldosterone-producing adenoma**
- Unilateral adrenal hyperplasia
- Adrenal carcinoma
- **Bilateral idiopathic adrenal hyperplasia**
- Bilateral macronodular adrenal hyperplasia
- Renin tumor (secondary aldosteronism)
- Aldosterone-producing tumors
- Renin responsive adenomas
- Familial forms:
  - Glucocorticoid-responsive aldosteronism (type 1)
  - Non-glucocorticoid-responsive aldosteronism (type II)

Note: The two disorders in bold account for the majority of cases of primary aldosteronism.

Causes of primary aldosteronism and their relevance to hypertension

PA is caused by several different types of adrenal gland hyperfunction that produce and secrete excess amounts of aldosterone secretion. Historically, a common cause of hyperaldosteronism was thought to be an aldosterone-producing adenoma (APA), which is a small (diameter <3 cm), solitary tumor that is monoclonal in origin. Broad screening of patients with hypertension has identified many more cases of PA, and from a variety of origins. Unilateral adrenal hyperplasia is an uncommon cause of PA. Bilateral idiopathic adrenal hyperplasia (IAH) causes PA, but usually has less severe hormonal and biochemical abnormalities when compared with other forms of adenoma.

There are also rare, genetic causes of PA. For example, a type of familial PA is caused by fusion of the 11-hydroxylase (*CYP11B1*) and the aldosterone synthase (*CYP11B2*) genes. The mutation produces a fusion protein with aldosterone synthase activity, which is expressed under adrenocorticotropic hormone (ACTH) stimulation in the zona fasciculata, resulting in a glucocorticoid-responsive form of bilateral PA.

Pathophysiological considerations

Disorders of PA are due to an excess of aldosterone secretion. Aldosterone acts by increasing the number of sodium channels on the luminal surface of epithelial cells in the distal nephron segment of the kidney, resulting in increased sodium reabsorption compared with the normal regulated state. Increased sodium reabsorption causes fluid retention and volume expansion and this is the primary mechanism behind elevated BP, which is present in all cases of PA. Hypertension caused by PA may vary in severity, ranging from very high levels (>200/120 mmHg) to mild levels. In all forms of PA, hypertension is typically resistant to treatment with commonly used antihypertensive drugs, except for aldosterone antagonists.

Volume expansion is not as severe as would be expected based solely on the plasma aldosterone concentration. This effect is limited by sodium escape or aldosterone escape, which reinstates the physiological balance between body sodium excretion and sodium intake, although the balance point is now higher. Therefore, fluid volumes are near normal and edema does not occur.

The mechanism of aldosterone escape is not completely understood. Excess volume triggers secretion of atrial natriuretic peptide (ANP); therefore, ANP is probably important for improving natriuresis response, but is not required for aldosterone escape. Increased volume due to fluid retention increases renal perfusion pressure, which causes increased natriuresis. Another factor is a decreased numbers of sodium chloride channels in the distal convoluted tubule, which reduces sodium reabsorption.

Excess aldosterone secretion contributes to development of hypokalemia. Excessive reabsorption of sodium creates increased negativity of the electrochemical potential across the luminal membrane of the kidney, thereby driving potassium loss. Just as with sodium and fluid balance, excessive potassium loss triggers mechanisms for potassium retention, mainly by blunting aldosterone synthesis, and a new balance between electrolyte intake and excretion

is established. The balance point will be lower than before (hypokalemia), but can be progressive. For example, a low-sodium diet in PA limits sodium reabsorption and hypokalemia. Loop diuretics may correct sodium retention, but they also exacerbate hypokalemia, and should be avoided in patients with PA.

Excess aldosterone levels may contribute to cardiovascular dysfunction. Clinical studies have demonstrated that patients with PA have significant cardiovascular damage, independent of age, BP level, and duration of hypertension. The relative rates of stroke (four times), atrial fibrillation (12 times), and MI (six times), as well as LVH and suden death, are all increased in patients with PA compared with patients with primary hypertension. Mineralocorticoid receptor antagonist therapy improves renal and cardiac function in patients with PA.

Clinical features and diagnosis

Several PA clinical manifestations help guide screening for PA (*Table 10.2*). The classical features are hypertension and hypokalemia. Metabolic alkalosis and hypomagnesemia may also occur. It is not uncommon to detect renal dysfunction such as proteinuria, increases in GFR, and renal cysts. Loss of skeletal muscle strength, muscle cramps, tetany, and fatigue occur and may progress to partial paralysis in severre forms of PA. Plasma renin levels are low in untreated patients. Resistant hypertension (persistence of hypertension with three antihypertensive medications) or discovery of adrenal incidentaloma in a patient with hypertension are additional indications for PA screening.

When further screening is indicated, one of the first steps is to repeatmeasurement of potassium levels in patients with hypokalemia. However, normokalemia does not exclude PA, as some patients are normokalemic unless exposed to a diuretic or a high-sodium diet.

The next measurement is PRA level. When this level is below normal (*Table 10.3*), the plasma aldosterone concentration (PAC) should be determined. The PAC:PRA ratio is an important screening test for PA. A PAC (ng/dl):PRA (ng/ml per hour)

Table 10.2. Clinical manifestations associated with primary aldosteronism.

- Hypertension
- Hypokalemia
- Muscle weakness
- Fatigue
- Reduced plasma renin
- Renal cysts
- Increased urine potassium
- Hypernatremia
- Metabolic alkalosis
- Hypomagnesemia
- Resistant hypertension

ratio greater than 20 suggests PA. For increased specificity, the PAC should be greater than 15 ng/dl and the PRA greater than 1 ng/ml per hour. Acceptance of the PAC:PRA ratio has led to an increased detection of PA as a secondary cause of hypertension.

Several additional tests are available after simple biochemical assays, including the saline loading test, in which the PAC level cannot be suppressed during sodium loading, confirming the diagnosis of PA. The intravenous saline suppression test consists of infusing 2 liters of saline over four hours and then measuring the PAC. PA is confirmed if the PAC remains greater than 10 ng/dl, although values of 5–10 ng/dl occur in bilateral PA. A 24-hour urine aldosterone level of greater than 12 µg on the third day of a high-salt diet (>150 mEq/day) also confirms the diagnosis (Figure 10.1).

After a biochemical diagnosis of PA is confirmed, the etiology should be sought. This is important because the treatment strategy will differ between unilateral and bilateral causes. Unilateral APAs are best managed by adrenalectomy, but they can be treated medically. Bilateral causes should be treated medically. In cases of PA where the patient is more than 30 years of age or has a family history of PA, a genetic cause should be suspected.

Localization and identification of subtype is performed using imaging techniques. Thin-slice CT scan is the first choice for localization (Figures 10.2–10.4, *Table 10.4*). MR imaging has lower resolution and sensitivity compared with CT scans. High-resolution CT scans detect adenomas in 90% of cases with this diagnosis. Detection of a solitary mass in the adrenal gland supports APA as the cause of PA, but the presence of a mass is not definitive. New scanners are so sensitive that they may detect many smaller nodules and signs of adrenal limb thickening. These signs may not be clinically relevant, but they may be mistaken for signs of bilateral disease or lead to misidentification of the wrong adrenal gland to target for intervention. In the case of a single, solitary mass more than 1 cm in diameter detected in a younger person, unilateral adenoma is diagnosed with certainty and surgery can be recommended without further diagnostic tests. Bilateral hyperplasia, however, cannot be diagnosed with imaging alone, because any one of the adrenal nodules can be the sole cause of PA.

Table 10.3. Initial screening tests for primary aldosteronism, showing typical values.

Test	Normal level	Indication of PA
Serum potassium	3.5–5.5 mEq/l	<3.6 mEq/l
Plasma renin activity (PRA)	1–3 ng/ml/hour	<1 ng/ml/hour
Plasma aldosterone concentration (PAC)	5–0 ng/dl	>15 ng/dl
PAC:PRA ratio	<10	>20 (80% sensitivity and specificity); >50 (strong evidence)

If these techniques fail to be definitive, adrenal venous sampling is the next step (Figure 10.5). This has long been considered the 'gold standard' for differentiation between unilateral and bilateral causes of PA. Adrenal venous sampling using percutaneous transfemoral bilateral adrenal vein catheterization is the best method

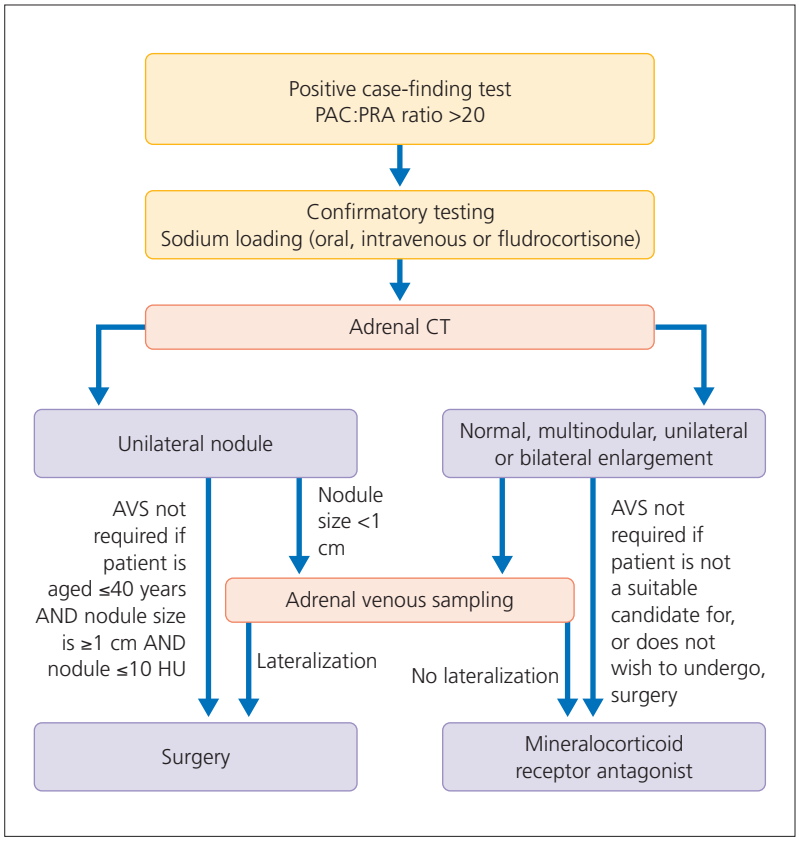


Fig. 10.1 Algorithm for using the ratio of plasma aldosterone concentration to plasma renin activity as a case-finding tool, and for subtype evaluation, of primary aldosteronism. This algorithm should be modified on the basis of clinical circumstance; common sense should prevail. AVS, adrenal vein sampling; HU, Hounsfield units; PAC, plasma aldosterone concentration; PRA, plasma renin activity. (Adapted from Mattsson C, Young W (2006) Primary aldosteronism: diagnostic and treatment strategies. *Nature Clin Prac Nephrol* **2(4):**198–208.)

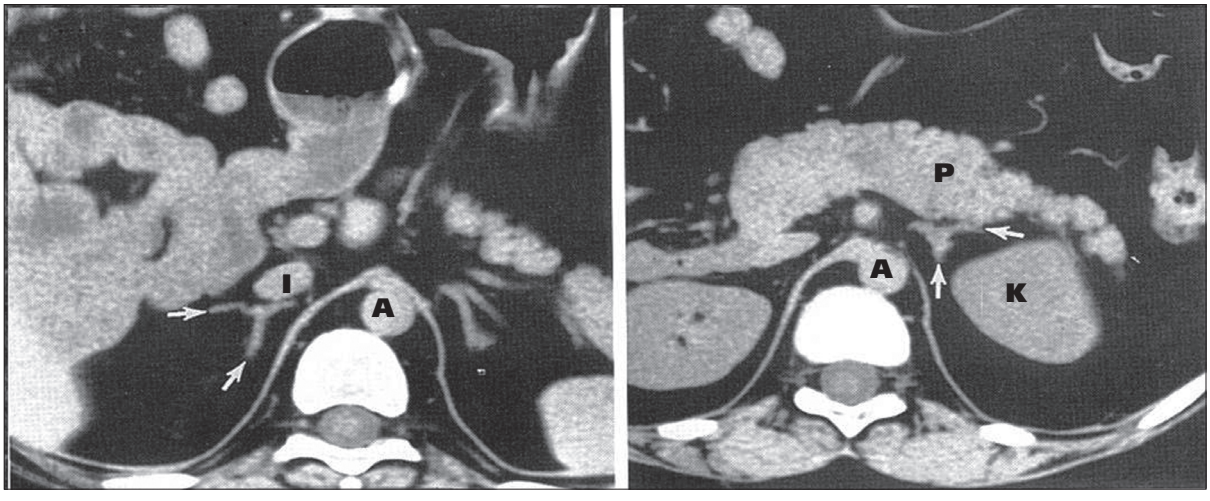


Fig. 10.2 CT scans showing normal adrenal glands (arrows). I, inferior vena cava; A, aorta; P, pancreas; K, kidney

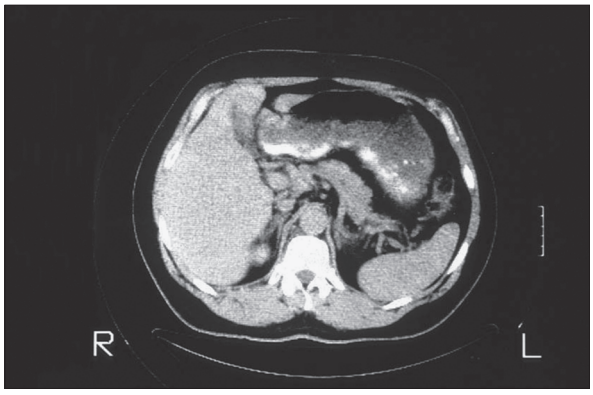


Fig. 10.3 CT scan showing bilateral adrenal gland hyperplasia.

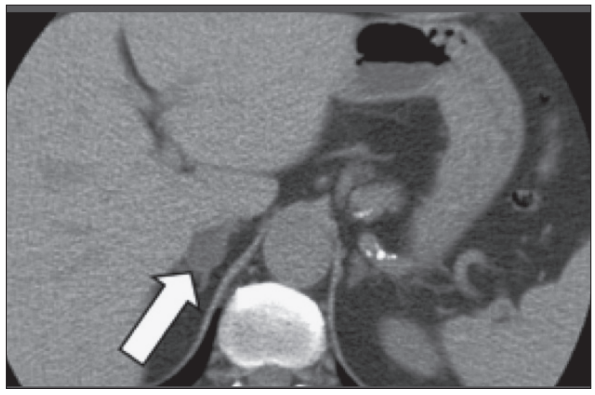


Fig. 10.4 CT scan showing a right adrenal gland tumor (adenoma) (arrow).

Table 10.4. Techniques used to localize and differentiate between unilateral and bilateral causes of primary aldosteronism.

Test	Advantages	Disadvantages
High-resolution CT	90% sensitivity for large APAs; accessible	False positives; contrast agents; small APAs not detected
MR imaging	Similar to CT; no contrast agent	More expensive; lower resolution
Adrenal venous sampling	95% success; 'gold standard'	Requires skill; catheter risks; contrast agents

for differentiating unilateral from bilateral disease. The ratios of aldosterone to cortisol in the two adrenal veins are compared, and a dominant side, in which the ratio is four times higher than the contralateral side (possibly lower), localizes aldersterone production to one adrenal gland.

This procedure is highly reliable when performed correctly. The main drawback of adrenal venous sampling is that the procedure requires an experienced angiographer, as cannulation of the right adrenal vein is difficult (on average only 75% successful), although some centers achieve rates greater than 90%. Complications are similar to all other types of vascular catheterization, and include hematomas, bleeding, stroke, MI, and venous dissection.

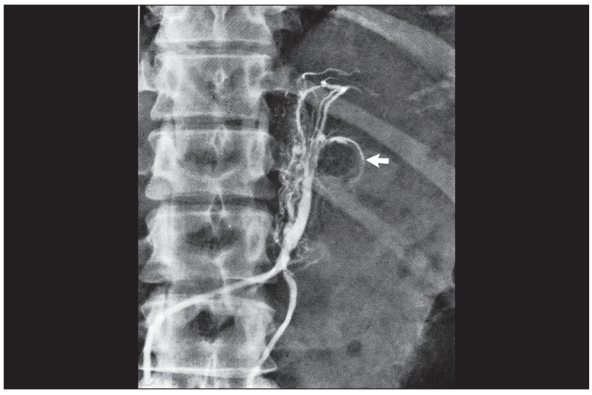


Fig. 10.5 Adrenal venogram showing a left adrenal gland tumor (adenoma) (arrow).

Treatment

Hypertension and hypokalemia can sometimes be controlled with medical treatment, but definitive therapy is preferred. Therefore, treatment goals for PA include control of BP, a return to normokalemia, and organ protection from excess aldosterone. The treatment of PA will depend on the pathology. Some types of PA are responsive to medical treatment while for others unilateral adrenalectomy is required.

Unilateral adenoma

Surgery is the recommended treatment for unilateral APAs as well as for the much rarer unilateral subtypes. Successful unilateral adrenalectomy normalizes aldosterone secretion and corrects hypokalemia in most cases. The BP usually improves but may not normalize after surgery.

Unilateral APAs are small tumors (and normally non-malignant) that can be removed by laparoscopy. This is the procedure of choice for adrenalectomy unless there are indications to the contrary. Laparoscopic procedures have many advantages over more invasive surgical techniques, primarily length of hospital stay and complications. Before surgery, patients may be treated with an aldosterone antagonist (i.e. spironolactone or eplerenone) to correct electrolyte disturbances.

Measurement of PAC determines when PA has been surgically corrected. A typical immediate result is hypoaldosteronism, which usually rapidly self-corrects and is not severe. Serum potassium levels should be measured weekly for at least one month, with potassium as needed.

BP levels should also be monitored. Hypertension can be cured or improved with removal of the unilateral adenoma over the following weeks to months; however, as many as 60% of patients have some residual hypertension, but lower then preoperative levels. Short duration of preoperative hypertension, lack of family history, young age, and better controlled BP are predictors of cure.

Long-term medical control is possible for unilateral APAs or other unilateral aldosterone-producing tumors. Surgery is recommended for compliance, but long-term outcomes are similar with medical therapy. Treatment goals are to control BP, improve hypokalemia, and protect the patient from harmful effects of PA. The effects of aldosterone excess are best treated with a mineralocorticoid receptor antagonist. With the co-administration of potassium supplements, spironolactone (doses ranging from 12.5 to 200 mg/day) is effective in normalizing potassium levels and BP. Eplerenone is a newer, more selective mineralocorticoid receptor antagonist that has a much lower binding affinity for progesterone and androgen receptors compared with spironolactone. Eplerenone causes fewer side-effects than spironolactone, but direct comparisons of efficacy and outcome for these drugs have not been published. BP control may require additional antihypertensive drugs, and lifestyle changes can aid in BP control. Hypokalemia is treated by diet, with limited sodium intake and potassium supplementation. If diuretics are required for BP control, potassium-sparing diuretics are indicated.

Bilateral hyperplasia

The goals for treating bilateral adrenal hyperplasia are the same as for unilateral APA, but the method is different. Bilateral IAH cases usually have less severe symptoms compared with patients with APA and may be easier to control with medical therapy. Medical strategy is the same, using a mineralocorticoid receptor antagonist (spironolactone or eplerenone) to normalize serum potassium levels, and treatment of hypertension. The addition of a low-dose thiazide diuretic may improve BP management and allow for lower doses of spironolactone, thereby reducing drug side-effects. The very rare genetic disorder, glucocorticoid-responsive aldosteronism, can be treated with exogenous glucocorticoid supplied at physiological levels and/or mineralocorticoid receptor antagonists.

CHAPTER 11

PHEOCHROMOCYTOMA

Overview

Pheochromocytomas are tumors that secrete catecholamines and other peptide hormones. Pheochromocytoma is a rare cause of hypertension, but are important to detect because tumor removal can be curative of hypertension as well as eliminating serious risks, especially sudden death, which can occur during extreme strees (such as pregnancy or surgery).

Pathophysiology/etiology

Pheochromocytomas are composed of chromaffin cells, which are neuroendocrine cells that synthesize and store catecholamines and other peptide hormones. Chromaffin cells are normally found mainly in the adrenal gland medulla and in sympathetic ganglia. Neoplasms that occur in the adrenal gland and are composed of this cell type are termed pheochromocytomas. Tumors that develop from chromaffin cells in sympathetic ganglia are termed paragangliomas (other names include extra-adrenal catecholamine-secreting paragangliomas and extra-adrenal pheochromocytomas). Although these tumor types share similarities, including the origin of the cell type that gives rise to the tumor, differences in nomenclature are useful in order to distinguish between the tumors because their risks of malignancy and genetic make-up are different.

The synthetic pathway of catecholamines begins with the amino acid tyrosine. Tyrosine is hydroxylated by tyrosine hydroxylase to 3,4-dihydro-phenylalanine (L-DOPA). A decarboxylation step converts this intermediate comppound into the neurotransmitter dopamine. Dopamine beta-hydroxylase acts on dopamine to make NE through a beta-oxidation step. NE is further converted into epinephrine through N-methylation by phenethylamine N-methyltransferase. In the adrenal medulla about 75% of NE is converted to epinephrine. These catecholamines are stored in the chromaffin cells. Chromaffin cell size determines the amount of catecholamine stored within and the cell's hormone secretory ability.

NE functions mostly in the SNS as a neurotransmitter; only small amounts are released into circulation by chromaffin cells to stimulate adrenergic receptors. Epinephrine acts more as a hormone. In response to stress, chromaffin cells in the adrenal medulla release epinephrine into the blood stream to prepare the body for the 'fight or flight' response. The actions of epinephrine and NE, via signaling through adrenergic receptors, lead to numerous physiological changes. For BP regulation, these changes include intense vasoconstriction and increases in CO.

The adrenergic response to catecholamines for BP regulation is covered in more detail in Chapter 3 (Primary or secondary hypertension).

Chromaffin cell populations that undergo expansion develop into tumors. Pheochromocytomas are rare. Estimates for the prevalence in the general population range from 0.0001 to 0.05% and pheochromocytoma is a relatively rare form of secondary hypertension, accounting for less than 0.2% of all cases. To date, the mechanisms involved in the formation of pheochromocytomas are poorly understood. Cases of bilateral pheochromocytomas often have a familial component, which accounts for about 10% of all pheochromocytomas. Bilateral pheochromocytomas are often associated with multiple endocrine neoplasia (MEN) types 2A and 2B or von Hippel–Lindau disease. In one study, a screen of non-selected patients with apparently sporadic pheochromocytomas and paragangliomas, found that 23% of the patients were carriers of different associated disorders, although most were more than 40 years old, and many of the tumors in the study were paragangliomas, in which underlying genetic conditions are relatively common. For this reason, it is recommended that every patient diagnosed with bilateral pheochromocytoma should undergo genetic testing for associated genetic disorders. Solitary, unilateral pheochromocytomas generally do not have any genetic component, although genetic testing for MEN 2A/2B is recommended because thyroid cancer is associted with this genetic abnormality and is fatal when untreated.

Pheochromocytomas produce and store many of the same hormones as occurs in normal the chromaffin cells. Regulation of pheochromocytoma hormone secretion, however, is abnormal and often, excess amounts are secreted. Hypertension is almost always a sign of larger pheochromocytomas because of their relatively inefficient secretion of catecholamines. Pheochromocytomas also secrete other types of peptide hormones, such as ACTH.

Over 90% of pheochromocytomas occur in the abdomen and most of these (85%) are in the adrenal glands. Adrenal pheochromocytomas are usually not malignant; only 10% metastasize, although 40% of extra-adrenal pheochromocytomas will metastasize. Malignant pheochromocytomas are generally slow-growing, and long survival is possible with medical treatment.

The exact nature of the pheochromocytoma-induced hypertension depends on what type of hormone is secreted by the tumor. Excess NE signals through alpha-adrenergic receptors, which causes vasoconstriction and diastolic hypertension. Epinephrine stimulates the beta-adrenergic receptors to increase CO and cause systolic hypertension. In some cases, pheochromocytomas may not release excess catecholamines; rather they release other hormones or multiple types of hormones. If the compounds in the catecholamine synthesis pathway, L-DOPA and dopamine, are secreted, vasodilation may occur, which may cause lowering of BP or limit hypertension due to catecholamine signaling.

Clinical signs

Pheochromocytomas usually present with several well-characterized clinical signs (*Table 11.1*) and their occurrence should raise clinical suspicion of the possible presence of a pheocromocytoma. These symptoms are important for a quick diagnosis, since this type of tumor is rare and not normally encountered. Elevated BP alone is insuficient evedence to justify additional testing, as fewer than 0.2% of hypertension cases are caused by excess catecholamine secretion.

The 'classic triad' of symptoms in patients with a pheochromocytoma is sweating, headache, and tachycardia. Almost 75% of patients with pheochromocytomas have this symptom complex. Headaches can be either mild or severe and are often intermittent and change in severity. However, the classic sympton triad is non-specific associated with many other disorders. Other common signs (>50% of cases) of pheochromocytomas include weight loss, pallor, and fundoscopic changes. Nausea, vomiting, and anxiety will are also frequent. Excess of catecholamines leads to a downregulation of the RAAS. Therefore, patients with pheochromocytoma are almost always volume depleted, which contributes to weight loss.

Hypertension is the most common clinical finding in a patient with pheochromocytoma; over 90% of pheochromocytomas result in hypertension. In about 50% the hypertension is sustained, as in essential hypertension. In the remainder the hypertension is paroxysmal. Between episodes of elevated BP, the BP may be normal, high, or low (superimposed paroxysmal hypertension). The periods of elevated BP vary in duration and severity. This variability is seen when comparing different patients and also when comparing different episodes in the same patient. Stimulation of a pheochromocytoma by an event may trigger paroxysmal hypertension. Such events include physical exercise, movement, drugs, or tobacco use. Stressors of pheochromocytomas are listed in *Table 11.2*, and conditions that mimic pheochromocytoma, either according to symptoms or elevated catecholamine levels, are listed in *Table 11.3*.

Table 11.1. Clinical signs associated with the presence of a pheochromocytoma.

- Hypertension
- Headache
- Sweating
- Tachycardia
- Pallor
- Nervousness
- Nausea
- Vomiting
- Weight loss
- Fundoscopic changes
- Anxiety
- Hyperglycemia
- Postural hypotension

Table 11.2. Some conditions that stimulate catecholamine production from pheochromocytomas.

- Physical exercise
- Anesthesia
- Tobacco use
- Glucagon excess
- Abdominal palpation
- Medications (see *Table 11.5*)

Table 11.3. Conditions that mimic pheochromocytomas and/or high catecholamine plasma levels.

- Acute pulmonary edema
- Eclampsia
- Hypertensive crises
- Diabetes mellitus
- Carcinoid syndrome
- Histamine excess
- Opiates
- Nicotine
- Monoamine oxidase inhibitors
- Stroke
- Seizures
- Brain tumors
- Anxiety
- Migraine headache
- Hypoglycemia

Diagnosis

Several tests can be performed for diagnosis a pheochromocytoma. Routine screening of the entire population or of all hypertensive patients is not recommended because of the rarity of this condition. Screening should only be performed in patients who have characteristic clinical features of pheochromocytoma and in instances in which an adrenal mass has been incidentally detected.

Currently, diagnosis is confirmed using plasma and urine measurements of catecholamine levels and catecholamine-derived metabolic products. Amounts measured in the urine and plasma are compared with 'normal' levels to predict the likelihood of a pheochromocytoma secreting the excess catecholamines (*Table 11.4*). Pharmacological tests may also be performed. A single grossly abnormal test is usually sufficient to establish a diagnosis, and values less than twice the upper limit of normal are inconclusive and are most often false-positive results.

The biochemical tests measure the amount of catecholamines (dopamine, NE, and epinephrine) or metabolites (metanephrine and normetanephrine) present in the body. In the past, urine-based tests were used because of the larger mass of samples collected compared with plasma samples. Tests using urine samples have good sensitivity and specificity (both over 98% for metanephrines) when the samples are collected over a 24-hour period (lower with single, 'spot' measurements). Older methods relied on fluorometric analysis for detection of metanephrines and catecholamines. While sensitive, their detection reagents gave both false-positive and false-negative results. More modern technologies are based on sample fractionation using liquid chromatography. Detection is based on electrochemical detection or tandem mass spectrometry; neither method has the high frequencies of false-positive and false-negative rates of the fluorometric assay and they are a large improvement in detection.

Plasma catecholamines should not be measured for diagnosis, but plasma metanephrine testing has excellent sensitivity but less specificity than urine catecholamines and metanephrines. A negative result for a plasma metanephrine test can be considered reliable, with high predictive value, and is superior to urine

testing. Plasma collection is easier than 24-hour urine collection, especially for children and non-compliant patients. The major drawback of plasma-based tests is a high false-positive rate. For hypertensive patients with no other indications of a pheochromocytoma, the false-positive rate has been reported to be more than 90%. This can lead to excessive healthcare costs (i.e. follow-up tests for localizing non-existent pheochromocytomas using CT scans or MR imaging) and excessive health risks (unnecessary radiation exposure and surgery).

There are a few situations that might interfere with plasma- or urine-based screens. Plasma-based measurement of total catecholamines has poor accuracy and is not reliable for screening, which is why plasma samples are limited to metanephrines. Any stressful situation, including illness or anxiety, alters catecholamine levels. Ideally, patients should not be taking any medications during sample collection, but only a few interfere with modern catecholamine and metanephrine measurements. Some medications that may interfere with biochemical measurements of catecholamine levels are listed in *Table 11.5*. Urine tests may be difficult to perform on patients with ESRD due to low urine output. Pharmacological-based tests, primarily the clonidine suppression test, can be used to confirm the diagnosis, but these are rarely performed because of the ease of measurement of plasma and urine levels. Clonidine (0.3 mg PO) should suppress plasma catecholamine levels to less than 500 pg/ml or metanephrine levels to less than 1 pmol/l within three hours.

Table 11.4. Biochemical assays used to screen for pheochromocytomas. Normal physiological ranges are included, along with the sensitivity and specificity associated with each assay.

Test	Normal range	Sensitivity	Specificity
Urine catecholamines	15–100 μg/day	83%	88%
Urine metanephrines	0–1.2 mg/day	76%	94%
Plasma catecholamines	Up to 1,200 pg/ml	85%	80%
Plasma metanephrines	30–170 pg/ml	99%	89%

Table 11.5. A partial list of medications that may interfere with biochemical measurements of catecholamine and metanephrine levels.

- 3,4-dihydro-phenylalanine (L-DOPA)
- Ethanol
- Acetaminophen
- Phenoxybenzamine
- Medications containing catecholamines
- Tricyclic antidepressants
- Clonidine withdrawal

The single most important concept in screening for pheochromocytoma is that symptom severity should be proportional to catecholamine excess. A patient with prominent sweating and tachycardia, but with metanephrines only twice the upper limit of normal, does not have pheochromocytoma as the cause of these symptoms, and another cause should be sought. Conversely, small (1–3 cm diameter) pheochromocytomas are often asymptomatic and yield normal test results, but these tumors may not be associated with hypertension or other symptoms.

Localizing a pheochromocytoma

After obtaining biochemical evidence to support the diagnosis of pheochromocytoma, imaging studies should be performed to localize the tumor (Figure 11.1, *Table 11.6*). Ninety-five percent of pheochromocytomas are found in the pelvis or abdomen and are large enough to be detected by MR imaging or a CT scan (Figure 11.2). This is especially true for sporadic pheochromocytomas, which are usually 3 cm or larger in diameter. Art the time of diagnosis both these imaging modalities have high sensitivity; CT scans are successful in detecting the tumor 93–100% of the time for adrenal pheochromocytomas and 90% for extra-adrenal tumors. CT scans are best performed with contrast agent, but this exposes patients to ionizing radiation, which is especially problematic in patients with renal insufficiency. MR imaging has good sensitivity and emits less radiation, but is more expensive than CT. Imaging characteristics, contrast uptake and washout, and heterogeneity on CT scans and MR images also differentiate pheochromocytomas from other types of adrenal gland tumors.

When clinical and biochemical evidence suggests a pheochromocytoma, but CT scanning or MR imaging is non-diagnostic, other types of tests should be used for detection/localization. One option is scintigraphy using ^{123}I-metaiodobenzylguanidine (MIBG) (Figure 11.3). MIBG is taken up by chromaffin cells and stored because it shares structural similarities with NE. This test has fair sensitivity and high specific, which CT scans and MR images lack. If MIBG scintigraphy fails, other types of scintigraphy or positron emission tomography can be considered, but these are still under evaluation for use in detection of pheochromocytomas.

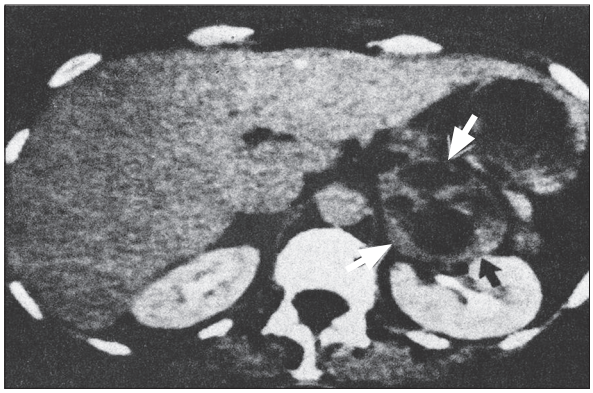


Fig. 11.2 CT scan showing a large pheochromocytoma (left adrenal gland) (arrows).

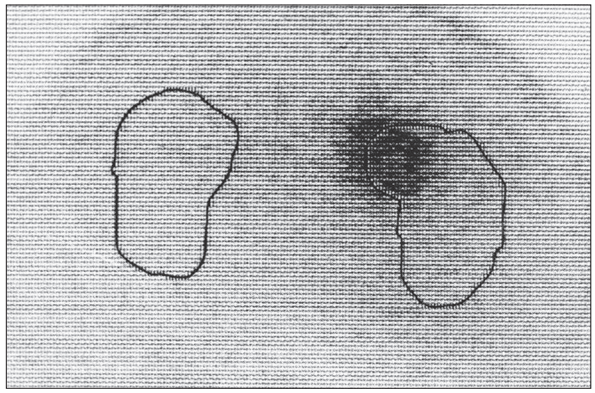


Fig. 11.3 Abnormal MIBG uptake in one of the adrenal glands suggestive of a pheochromocytoma.

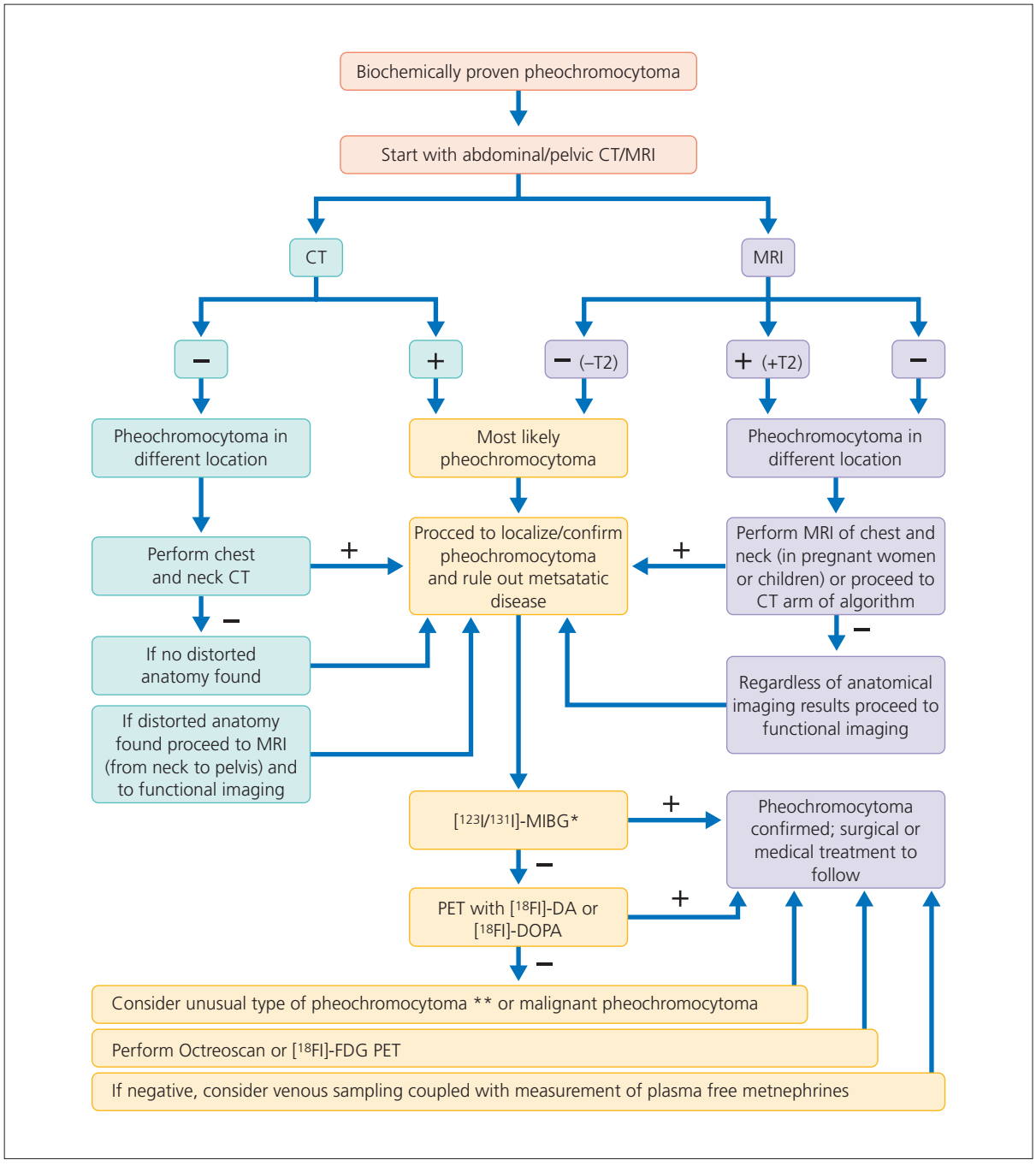


Fig. 11.1 Algorithm for diagnostic localization of a pheochromocytoma. CT, computed tomography; MRI, magnetic resonance imaging; PET, position emission tomography; FDG, flurodeoxyglucose; (+T2), positive T1- and T2-weighted MRI examinations; (−T2), positive T1- and negative T2-weighted MRI examinations; +, examination positive for tumor; −, examination negative for tumor; *, ^{123}I-MIBG scintigraphy preferred over ^{131}I-MIBG scintigraphy, where available; **, unusual types of pheochromocytomas may not express the norepinephrine transporter system or may have a low number of catecholamine storage granules. (Adapted from Ilias I, Pacak K (2004) Current approaches and recommended algorithm for the diagnostic localization of pheochromocytoma. *J Clin Endocrinol Metab* **89(2):**479–491.)

Table 11.6. Imaging studies used for localizing pheochromocytomas.

Test	Advantages	Disadvantages
High resolution CT scanning	93–100% sensitivity; accessible	False positives; contrast agent
MR imaging	Similar to CT; no contrast agent	More expensive; lower resolution
Scintigraphy using ^{123}I-metaiodobenzylguanidine	High specificity	Reduced availability

Treatment

The recommended treatment for a pheochromocytoma is surgery, after appropriate preoperative medical preparation to minimize risks.

Therapy to control hypertension and restore fluid levels is crucial in the preoperative period. These steps are important to prevent TOD due to elevated BP. The main goals of surgical preparation are restoration of fluid and electrolyte status and blockade of adrenergic receptors to prevent catecholamine surges during surgery.

Very high BP levels should be lowered with intravenous phentolamine, an alpha-adrenergic receptor blocker, but this is rarely necessary. Once the BP is stable, oral treatment should be given. Adrenergic receptor blockade starts with an alpha-adrenergic receptor blocker administered 2–4 weeks before surgery. The goal is to reduce the BP to approximately 140/90 mmHg and allow volume repletion. Phenoxybenzamine is usually the preferred drug; it is a non-selective and irreversible alpha-adrenergic blocker that is administered at increasing doses of 10–40 mg BID. The non-selective nature means that the alpha$_2$ receptor is also blocked, removing the NE feedback loop, which may cause tachycardia that subsequently requires a beta-blocker, but this is not usually a problem because the treatment is relatively short-term. Other specific and reversible alpha-receptor blockers, such as doxazosin and terazosin, may be used for patients with milder catecholamine excess.

Metyrosine has also been used for preoperative medical treatment. Metyrosine inhibits tyrosine hydroxylase and catecholamine synthesis. It can be effective, but has a number of side-effects, some of which may be disabling, especially with long-term administration. It is normally used only if adrenergic blockade cannot be used or in severe catecholamine excess.

Because of the risk of perioperative mortality, surgery should be performed by an experienced surgical team. Adrenalectomy is increasingly being performed with laparoscopy, which generally decreases patient stress because operative time is shorter and blood loss is less. Hospital stays are, on average, less than half as long for laparoscopic surgery compared with open abdominal surgery. However, laparoscopic approaches are not always available. Multiple tumors, large tumors (>6 cm diameter), and localization to areas other than the adrenal gland may make laparoscopic surgery difficult or impossible. Improvements in imaging studies are decreasing the need for exploratory surgery. Malignant tumors may require chemotherapy in addition to surgical removal.

The long-term prognosis after surgery to remove a pheochromocytoma is good. Long-term monitoring is recommended, as the tumor recurs in a small percentage of patients and new primary tumors may occur in patients with genetic diseases such as MEN 2A.

BP is almost always improved with a successful procedure. However, there are reports of large swings in BP levels during or just after pheochromocytoma removal. Elevations in BP that occur during surgery are probably the result of a large increase in catecholamine production due to provoking, handling, or deoxygenating the tumor. The large reduction in catecholamine levels after tumor removal may lead to hypotension, particularly in the presence of adrenergic blockade. High levels of adrenergic signaling prior to surgery downregulate the RAAS and the RAAS may not respond to the almost immediate decrease in catecholamines and vasodilation that occur after surgery, particularly when volume depletion has not been corrected. Postoperative hypoglycemia is rare but may occur one or more days post surgery due to decreased levels of catecholamines, which normnally decrease insulin signaling and increase glucose production.

Further reading

Chapter 1

Balu S (2009) Estimated annual direct expenditures in the United States as a result of inappropriate

Chobanian AV, Bakris HR, Black WC *et al.* (2003) The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7). *JAMA* **289(19):**2560–2572.

Fischer MA, Avorn J (2004) Economic mplications of evidence-based prescribing for hypertension: can better care cost less? *JAMA* **291(15):**1850–1856.

Gaziano TA, Bitton A, Anand S *et al.* (2009) The global cost of non-optimal blood pressure. *J Hypertens* **27(7):**1472–1477.

Greenlund KJ, Croft JB, Mensah GA (2004) Prevalence of heart disease and stroke risk factors in persons with prehypertension in the United States, 1999–2000. *Arch Intern Med* **164(19):**2113–2118.

Hodgson TA, Cai L (2001) Medical care expenditures for hypertension, its complications, and its comorbidities. *Med Care* **39(6):**599–615.

Hodgson TA, Cohen AJ (1999) Medical care expenditures for selected circulatory diseases: opportunities for reducing National Health expenditures. *Med Care* **37(10):**994–1012.

Hsia J, Margolis KL, Eaton CB *et al.* (2007) Prehypertension and cardiovascular disease risk in the Women's Health Initiative. *Circulation* **115(7):**855–860.

Jackson CM, Lawes DA, Bennett RJ *et al.* (2005) Treatment with drugs to lower blood pressure and blood cholesterol based on an individual's absolute cardiovascular risk. *Lancet* **365(9457):**434–441.

Kaplan NM (2002) *Kaplan's Clinical Hypertension*, 8th edn. Lippincott Williams & Wilkins, Philadelphia.

Lewington SR, Clarke R, Qizilbash N *et al.* (2002) Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* **360(9349):**1903–1913.

Miura K, Daviglus ML, Dyer AR *et al.* (2001) Relationship of blood pressure to 25-year mortality due to coronary heart disease, cardiovascular diseases, and all causes in young adult men: the Chicago Heart Association Detection Project in Industry. *Arch Intern Med* **161(12):**1501–1508.

Psaty BM, Furberg CD, Kuller LH *et al.* (2001) Association between blood pressure level and the risk of myocardial infarction, stroke, and total mortality: the Cardiovascular Health Study. *Arch Intern Med* **161(9):**1183–1192.

Vakili BA, Okin PM, Devereux RB (2001) Prognostic implications of left ventricular hypertrophy. *Am Heart J* **141(3):**334–341.

Van den Hoogen PC, Feskens EJ, Nagelkerke NJ (2000) The relation between blood pressure and mortality due to coronary heart disease among men in different parts of the world. Seven Countries Study Research Group. *N Engl J Med* **342(1):**1–8.

Vasan RS, Beiser A, Seshadri S (2002) Residual lifetime risk for developing hypertension in middle-aged women and men: the Framingham Heart Study. *JAMA* **287(8):**1003–1010.

Wolf-Maier K, Cooper RS, Banegas JR *et al.* (2003) Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. *JAMA* **289(18):**2363–2369.

Chapter 2

Beevers G, Lip GY, O'Brien E (2001) ABC of hypertension: blood pressure measurement. Part II. Conventional sphygmomanometry: technique of auscultatory blood pressuremeasurement. *BMJ* **322(7293):**1043–1047.

Canzanello VJ, Jensen PL, Schwartz GL (2001) Are aneroid sphygmomanometers accurate in hospital and clinic settings? *Arch Intern Med* **161(5):**729–731.

Chobanian AV, Bakris HR, Black WC *et al.* (2003) The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7). *JAMA* **289(19):**2560–2572. (*Hypertension* **42(6):**1206–1252)

Clement DL, De Buyzere ML, De Bacquer DA *et al.* (2003) Prognostic value of ambulatory blood pressure recordings in patients with treated yypertension. *N Engl J Med* **348(24):**2407–2415.
Dolan E, Stanton A, Thijs L *et al.* (2005) Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: the Dublin Outcome Study. *Hypertension* **46(1):**156–161.
Hsia J, Margolis KL, Eaton CB *et al.* (2007) Prehypertension and cardiovascular disease risk in the Women's Health Initiative. *Circulation* **115(7):**855–860.
Imai Y, Otsuka K, Kawano Y *et al.* (2003) Japanese Society of Hypertension (JSH) Guidelines for Self-Monitoring of Blood Pressure at Home. *Hypertens Res* **26(10):**771–782.
Jones DW, Appel LJ, Sheps SG *et al.* (2003) Measuring blood pressure accurately: new and persistent challenges. *JAMA* **289(8):**1027–1030.
Klungel OH, de Boer A, Paes AH *et al.* (2000) Influence of correction for within-person variability in blood pressure on the prevalence, awareness, treatment, and control of hypertension. *Am J Hypertens* **13(1):**88–91.
Ma G, Sabin N, Dawes M (2008) A comparison of blood pressure measurement over a sleeved arm versus a bare arm. *CMAJ* **178(5):**585–589.
Mancia G, De Backer G, Dominiczak A *et al.* (2007) 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* **25(6):**1105–1187.
Mengden T, Chamontin B, Phong Chau N *et al.* (2000) User procedure for self-measurement of blood pressure. First International Consensus Conference on Self Blood Pressure Measurement. *Blood Press Monit* **5(2):**111–129.
Niiranen TJ, Kantola IM, Vesalainen R *et al.* (2006) A comparison of home measurement and ambulatory monitoring of blood pressure in the adjustment of antihypertensive treatment. *Am J Hypertens* **19(5):**468–474.
O'Brien E, Asmar R, Beilin L *et al.* (2005) Practice guidelines of the European Society of Hypertension for clinic, ambulatory and self blood pressure measurement. *J Hypertens* **23(4):**697–701.
Pickering TG, Hall JE, Appel LJ *et al.* (2005) Recommendations for blood pressure measurement in humans and experimental animals: Part 1: Blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on high blood pressure research. *Circulation* **111(5):**697–716.
Pickering TG, White WB (2008) Ash Position Paper: Home and ambulatory blood pressure monitoring. When and how to use self (home) and ambulatory blood pressure monitoring. *J Clin Hypertens (Greenwich)* **10(11):**850–855.
Tholl U, Forstner K, Anlauf M (2004) Measuring blood pressure: pitfalls and recommendations. *Nephrol Dial Transplant* **19(4):**766–770.
U.S. Preventive Services Task Force (2007) Screening for for high blood pressure. U.S. Preventive Services Task Force reaffirmation recommendation statement. *Ann Intern Med* **147(11):**783–786.
Wang JG, Staessen JA, Messaggio E *et al.* (2003) Salt, endogenous ouabain and blood pressure interactions in the general population. *J Hypertens* **21(8):**1475–1481.
Watson RD, Lumb R, Young MA *et al.* (1987) Variation in cuff blood pressure in untreated outpatients with mild hypertension: implications for initiating antihypertensive treatment. *J Hypertens* **5(2):**207–211.
Williams B, Poulter NR, Brown MJ *et al.* (2004) Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004 – BHS IV. *J Hum Hypertens* **18(3):**139–185.

Chapter 3

Adrogue HJ, Madias NE (2007) Sodium and potassium in the pathogenesis of hypertension. *N Engl J Med* **356(19):**1966–1978.
Ahmed SB, Fisher ND, Stevanovic R *et al.* (2005) Body mass index and angiotensin-dependent control of the renal circulation in healthy humans. *Hypertension* **46(6):**1316–1320.
Burns KD, Li N (2003) The role of angiotensin II-stimulated renal tubular transport in hypertension. *Curr Hypertens Rep* **5(2):**165–171.
Chen J, Gu D, Huang J *et al.* (2009) Metabolic syndrome and salt sensitivity of blood pressure in non-diabetic people in China: a dietary intervention study. *Lancet* **373(9666):**829–835.
de Simone, Devereux RB, Chinali M *et al.* (2004) Risk factors for arterial hypertension in adults with initial optimal blood pressure: the Strong Heart Study. *Hypertension* **47(2):**162–167.
de Wardener HE, He FJ, MacGregor GA (2004) Plasma sodium and hypertension. *Kidney Int* **66(6):**2454–2466.

Halperin RO, Sesso HD, Ma J *et al.* (2006) Dyslipidemia and the risk of incident hypertension in men. *Hypertension* **47(1):**45–50.
Lavoie JL, Sigmund CD (2003) Minireview: overview of the renin-angiotensin system – an endocrine and paracrine system. *Endocrinology* **144(6):**2179–2183.
Moore LL, Visioni AJ, Qureshi MM *et al.* (2005) Weight loss in overweight adults and the long-term risk of hypertension: The Framingham Study. *Arch Intern Med* **165(11):**1298–1303.
Neter JE, Stam BE, Kok FJ, Grobbee DE *et al.* (2003) Influence of weight reduction on blood pressure: a meta-analysis of randomized controlled trials. *Hypertension* **42(5):**878–884.
Obarzanek E, Proschan MA, Vollmer WM *et al.* (2003) Individual blood pressure responses to changes in salt intake: results from the DASH-Sodium trial. *Hypertension* **42(4):**459–467.
Pacak K, Linehan WM, Eisenhofer G *et al.* (2001) Recent advances in genetics, diagnosis, localization, and treatment of pheochromocytoma. *Ann Intern Med* **134(4):**315–329.
Parish JM, Somers VK (2004) Obstructive sleep apnea and cardiovascular disease. *Mayo Clin Proc* **79(8):**1036–1046.
Poirier P, Giles TD, Bray GA *et al.* (2006) Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. *Circulation* **113(6):**898–8918.
Rana BK, Insel PA, Payne SH *et al.* (2007) Population-based sample reveals gene-gender interactions in blood pressure in white Americans. *Hypertension* **49(1):**96–106.
Schillaci G, Pasqualini L, Vaudo G *et al.* (2003) Effect of body weight changes on 24-hour blood pressure and left ventricular mass in hypertension: a 4-year follow-up. *Am J Hypertens* **16(8):**634–639.
Schmidlin O, Sebastian AF, Morris RC Jr. (20070 What initiates the pressor effect of salt in salt-sensitive humans? Observations in normotensive blacks. *Hypertension* **49(5):**1032–1039.
Staessen JA, Wang J, Bianchi G *et al.* (2003) Essential hypertension. *Lancet* **361(9369):**1629–1641.
van Paassen P, de Zeeuw D, de Jong PE *et al.* (2000) Renin inhibition improves pressure natriuresis in essential hypertension. *J Am Soc Nephrol* **11(10):**1813–1818.
Waeber B, Brunner H, Burnier M *et al.* (2007) Hypertension. In: *Cardiovascular Medicine*, 3rd edn. (eds JT Willerson, JN Cohn, HJJ Wellens *et al.*) Springer-Verlag, London, pp. 1833–1870.
Wang NY, Young JH, Meoni LA *et al.* (2008) Blood pressure change and risk of hypertension associated with parental hypertension: The Johns Hopkins Precursors Study. *Arch Intern Med* **168(6):**643–648.
Wilson PW, D'Agostino RB, Sullivan L *et al.* (2002) Overweight and obesity as determinants of cardiovascular risk: The Framingham Experience. *Arch Intern Med* **162(16):**1867–1872.

Chapter 4

Appel LJ, Espeland MA, Easter L *et al.* (2001) Effects of reduced sodium intake on hypertension control in older individuals: results from the trial of nonpharmacologic interventions in the elderly (Tone). *Arch Intern Med* **161(5):**685–693.
Appel LJ, Moore TJ, Obarzanek E *et al.* (1997) A clinical trial of the effects of dietary patterns on blood pressure. Dash Collaborative Research Group. *N Eng J Med* **336:**1117–1124.
Barengo NC, Hu G, Kastarinen M *et al.* (2005) Low physical activity as a predictor for antihypertensive drug treatment in 25–64-year-old populations in eastern and south-western Finland. *J Hypertens* **23(2):**293–299.
Beulens JW, Rimm EB, Ascherio A *et al.* (2007) Alcohol consumption and risk for coronary heart disease among men with hypertension. *Ann Intern Med* **146(1):**10–19.
Dickinson HO, Mason JM, Nicolson DJ *et al.* (2006) Lifestyle interventions to reduce raised blood pressure: a systematic review of randomized controlled trials. *J Hypertens* **24(2):**215–233.
Graudal NA, Galloe AM, Garred P (1998) Effect of sodium restriction on blood pressure, renin, aldosterone, catecholamines, cholesterols, and triglyceride: a meta-analysis. *JAMA* **279:**1383–1391.
Kaplan NM (2002) *Kaplan's Clinical Hypertension*, 8th edn. Lippincott Williams & Wilkins, Philadelphia.
Midgley JP, Matthew AG, Greenwood CM *et al.* (1996) Effect of reduced dietary sodium on blood pressure: a meta-analysis of randomised controlled trials. *JAMA* **275:**1590–1597.
Moore LL, Visioni AJ, Qureshi MM *et al.* (2005) Weight loss in overweight adults and the long-term risk of hypertension: The Framingham Study. *Arch Intern Med* **165(11):**1298–1303.

Nakanishi N, Yoshida H, Nakamura K *et al.* (2001) Alcohol consumption and risk for hypertension in middle-aged Japanese men. *J Hypertens* **19(5):**851–855.

Stamler J, Liu K, Ruth KJ *et al.* (2002) Eight-year blood pressure change in middle-aged men: relationship to multiple nutrients. *Hypertension* **39(5):**1000–1006.

Stamler R, Stamler J, Gosch FC *et al.* (1989) Primary rrevention of hypertension by nutritional-hygienic means. Final report of a randomized, controlled trial. *JAMA* **262(13):**1801–1807.

Stewart KJ, Bacher AC, Turner KL *et al.* (2005) Effect of exercise on blood pressure in older persons: a randomized controlled trial. *Arch Intern Med* **165(7):**756–762.

Stolarz-Skrzypek K, Kuznetsova T, Thijs L *et al.* (2011) Fatal and nonfatal outcomes, incidence of hypertension, and blood pressure changes in relation to urinary sodium excretion. *JAMA* **305(17):**1777–1785.

Taubes G (1998) The (political) science of salt. *Science* **281:**898–907.

Taylor RS, Ashton KE, Moxham T *et al.* (2011) Reduced dietary salt for the prevention of cardiovascular disease: a meta-analysis of randomized controlled trials (Cochrane Review). *Am J Hypertens* **24:**843–853.

Whelton SP, Chin A, Xin X *et al.* (2002) Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. *Ann Intern Med* **136(7):**493–503.

Xin X, He J, Frontini MG *et al.* (2001) Effects of alcohol reduction on blood pressure: a meta-analysis of randomized controlled trials. *Hypertension* **38(5):**1112–1117.

Chapter 5

ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group (2002) Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* **288:**2981–2997.

ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group (2003) Diuretic versus alpha-blocker as first-step antihypertensive therapy: final results from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Hypertension* **42:**239–246.

American Diabetes Association (2010) Executive summary: Standards of medical care in diabetes – 2010. *Diabetes Care* **33:**S4–S10.

Arguedas JA, Perez MI, Wright JM (2009) Treatment blood pressure targets for hypertension. *Cochrane Database Syst Rev* **3**:CD004349.

Brenner BM, Cooper ME, de Zeeuw D *et al.* (2001) Effects of losartan on renal and cardiovascular outcomes in patients with Type 2 diabetes and nephropathy. Reduction of Endpoints in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) Study Group. *N Engl J Med* **345:**861–869.

Chobanian AV, Bakris GL, Black HR *et al.* (2003) Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. National High Blood Pressure Education Program Coordinating Committee. *Hypertension* **42:**1206–1252.

Cooper WO, Hernandez-Diaz S, Arbogast PG *et al.* (2006) Major congenital malformations after first-trimester exposure to ACE inhibitors. *N Engl J Med* **354:**2443–2451.

Dahlöf B, Sever PS, Poulter NR *et al.* (2005) Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm (ASCOT–BPLA): a multicentre randomised controlled trial. *Lancet* **366:**895–906.

Elliott WJ, Basu S, Meyer PM (2008) Initial drugs for heart failure prevention in hypertensive patients: Network and Bayesian meta-analyses of clinical trial data (abstract). *Circulation* **118(Suppl. 2)**:S886.

Elliott WJ, Basu S, Meyer PM (2009) Initial drugs for coronary heart disease prevention in hypertensive patients: Network and Bayesian meta-analyses of clinical trial data (abstract). *J Clin Hypertens (Greenwich)* **11(Suppl. A)**:A7.

Elliott WJ, Basu S, Meyer PM (2009) Initial drugs for stroke prevention in hypertensive patients: Network and Bayesian meta-analyses of clinical trial data (abstract). *J Clin Hypertens (Greenwich)* **11(Suppl. A)**:A7.

Elliott WJ, Grimm RH Jr. (2008) How to use diuretics in clinical practice – one opinion. *J Clin Hypertens (Greenwich)* **10:**856–862.

Hackman DG, Khan NA, Hemmelgarn BR *et al.* (Canadian Hypertension Education Program) (2010) The 2010 Canadian Hypertension Education Program recommendations for the management of hypertension: part 2 – therapy. *Can J Cardiol* **26(5):**249–258.

Jamerson K, Weber MA, Bakris GL *et al.*, ACCOMPLISH Trial Investigators (2008) Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med* **359:**2417–2428.

Julius S, Kjeldsen S, Weber M *et al.* (2004) Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: The VALUE randomised trial. *Lancet* **363:**2022–2031.

Law MR, Morris JK, Wald NJ (2009) Use of blood pressure lowering drugs in the prevention of cardiovascular disease: Meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ* **338:**b1665 doi:101136/bmj.b1665.

Levey AS, Rocco MV, Anderson S *et al.* (2004) K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis* **43 (Suppl. 1)**:S1–S290.

Lewis EJ, Hunsicker LG, Clarke WR *et al.* (2001) Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to Type 2 diabetes. Collaborative Study Group. *N Engl J Med* **345:**851–860.

Lindholm LH, Carlberg B, Samuelsson O (2005) Should β-blockers remain first choice in the treatment of primary hypertension? A meta-analysis. *Lancet* **366:**1545–1553.

Littlejohns P, Ranson P, Sealey C *et al.* (for the National Collaborating Centre for Chronic Conditions) (2006) Hypertension: management of hypertension in adults in primary care (partial update of NICE Clinical Guideline 18). National Institute for Health and Clinical Excellence. www.nice.org.uk/page.aspx?o=278167, accessed June 25th 2006.

Maggioni AP, Anand I, Gottlieb SO *et al.* (2002) Val-HeFT Investigators (Valsartan Heart Failure Trial). Effects of valsartan on morbidity and mortality in patients with heart failure not receiving angiotensin-converting enzyme inhibitors. *J Am Coll Cardiol* **40:**1414–1421.

Mancia G, De Backer G, Dominiczak A *et al.* (2007) Guidelines for the management of arterial hypertension. Task Force for the Management of Arterial Hypertension of the European Society of Hypertension and the European Society of Cardiology. *J Hypertens* **25:**1105–1187.

Materson BJ, Reda DJ, Cushman WC (1995) Department of Veterans Affairs single-drug therapy of hypertension study. Revised figures and new data. Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. *Am J Hypertension* **8:**189–192.

McMurray JJV, Östergren J, Swedberg K *et al.* (2003) Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: The CHARM-Added trial. CHARM Investigators and Committees. *Lancet* **362:**767–771.

McMurray JJV, Pitt B, Latini R *et al.*, ALOFT Investigators (2008) Effects of the oral direct renin inhibitor aliskiren in patients with symptomatic heart failure. *Circulation: Heart Fail* **1:**17–24.

ONTARGET Investigators (2008) Telmisartan, ramipril or both in patients at high risk for vascular events. *N Engl J Med* **8:**1547–1549.

Oparil S, Yarows SA, Patel S *et al.* (2007) Efficacy and safety of combined use of aliskiren and valsartan in patients with hypertension: a randomised, double-blind trial. *Lancet* **370:**221–229.

Pahor M, Psaty BM, Alderman MH *et al.* (2000) Health outcomes associated with calcium antagonists compared with other first-line antihypertensive therapies: a meta-analysis of randomised controlled trials. *Lancet* **356:**1949–1951.

Parving HH, Brenner BM, McMurray JJV *et al.* (2009) Aliskiren trial in type 2 diabetes using cardio-renal endpoints (ALTITUDE): rationale and study design. *Nephrol Dial Transplant* **24(5):**1663–1671.

Parving H-H, Persson F, Lewis JB *et al.*, for the AVOID Study Investigators (2008) Aliskiren combined with losartan in type 2 diabetes and nephropathy. *N Engl J Med* **358:**2433–2446.

Prospective Studies Collaborative (2002) Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* **360:**1903–1913.

Psaty BM, Heckbert SR, Koepsell TD *et al.* (1995) The risk of myocardial infarction associated with antihypertensive drug therapies. *JAMA* **274:**620–625.

Quinn RR, Hemmelgarn BR, Padwal RS *et al.* (Canadian Hypertension Education Program) (2010) The 2010 Canadian Hypertension Education Program recommendations for the management of hypertension: part 1 – blood pressure measurement, diagnosis and risk assessment. *Can J Cardiol* **26(5):**241–248.

Ram CVS, Wali M (2013) Renal denervation in resistant hypertension: an emerging novel therapy. *J Clin Prev Cardiol* **2:**73–83.

Rosendorff C, Black HR, Cannon CP *et al.* (2007) Treatment of hypertension in the prevention and management of ischemic heart disease. A Scientific Statement from the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention. *Circulation* **115:**2761–2788.

Solomon SD, Appelbaum E, Manning WJ *et al.*, ALLAY Trial Investigators (2009) Effect of the direct renin inhibitor, aliskiren, the angiotensin receptor blocker, losartan, or both, on left ventricular mass in patients with hypertension and left ventricular hypertrophy. *Circulation* **119:**530–527.

The ACCORD Study Group, Cushman WC, Evans GW, Byington RP *et al.* (2010) Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* **362(17):**1575–1585.

Turnbull F (for the Blood Pressure Lowering Treatment Trialists' Collaboration) (2003) Effects of different blood pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet* **362:**1527–1535.

Turnbull F, Neal B, Ninomiya T *et al.*, Blood Pressure Lowering Treatment Trialists' Collaboration (2008) Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: a meta-analysis of randomised trials. *BMJ* **336:**1121–1123.

Turnbull F, Neal B, Pfeffer M *et al.*, Blood Pressure Lowering Treatment Trialists' Collaboration (2007) Blood pressure-dependent and independent effects of agents that inhibit the renin-angiotensin system. *J Hypertens* **25:**951–958.

Verdecchia P, Reboldi G, Angeli F *et al.* (2005) Angiotensin-converting enzyme inhibitors and calcium channel blockers for coronary heart disease and stroke prevention. *Hypertension* **46:**386–392.

Wald DS, Law M, Morris JK *et a*l. (2009) Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. *Am J Med* **122:**290–300.

Wall GC, Gibner D, Craig S (2003) Ethacrynic acid and the sulfa-sensitive patient. *Arch Intern Med* **163:**116–117.

Wiysong CS, Bradley H, Mayosi B *et al.* (2007) Beta-blockers for hypertension. *Cochrane Database Syst Rev* **1**:CD002003.

Yusuf S, Diener H-C, Sacco R *et al.*, PRoFESS Study Group (2008) Telmisartan to prevent recurrent stroke and cardiovascular events. *N Engl J Med* **359:**1225–1237.

Yusuf S, Telmisartan Randomised Assessment Study in ACE Intolerant subjects with cardiovascular Disease (TRANSCEND) Investigators (2008) Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. *Lancet* **371:**1174–1183.

Chapter 6

Aggarwal M, Khan IA (2006) Hypertensive crisis: hypertensive emergencies and urgencies. *Cardiol Clin* **24(1):**135–146.

Archer SL, Huang JM, Hampl V *et al.* (1994) Nitric oxide and cGMP cause vasorelaxation by activation of a charybdotoxin-sensitive K channel by cGMP-dependent protein kinase. *Proc Natl Acad Sci USA* **91(16):**7583–7587.

Aronson S, Dyke CM, Stierer KA *et al.* (2008) The Eclipse Trials: comparative studies of clevidipine to nitroglycerin, sodium nitroprusside, and nicardipine for acute hypertension treatment in cardiac surgery patients. *Anesth Analg* **107(4):**1110–1121.

Brott T, Bogousslavsky J (2000) Treatment of acute ischemic stroke. *N Engl J Med* **343(10):**710–722.

Chobanian AV, Bakris GL, Black HR *et al.* (2003) The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7). *JAMA* **289(19):**2560–2572.

Fenves AZ, Ram CV (2005) Drug treatment of hypertensive urgencies and emergencies. *Semin Nephrol* **25(4):**272–280.

Gubitz G, Sandercock P (2000) Acute ischaemic stroke. *BMJ* **320(7236):**692–696.

Handler J (2006) Hypertensive urgency. *J Clin Hypertens (Greenwich)* **8(1):**61–64.

Joint ESH/ESC Guidelines (2013) Guidelines for the management of arterial hypertension. *Eur Heart J* **34(28):**2159–2219.

Kaplan NM (2002) *Kaplan's Clinical Hypertension*, 8th edn. Lippincott Williams & Wilkins, Philadelphia.

Lip GY, Beevers M, Beevers DG (2000) Do patients with de novo hypertension differ from patients with previously known hypertension when malignant phase hypertension occurs? *Am J Hypertens* **13(8):**934–939.

Lip GY, Beevers M, Beevers DG (1997) Does renal function improve after diagnosis of malignant phase hypertension? *J Hypertens* **15(11):**1309–1315

Murphy C (1995) Hypertensive emergencies. *Emerg Med Clin North Am* **13(4):**973–1007.

Nadar S, Beevers DG, Lip GYH (2005) Echocardiographic changes in patients with malignant phase hypertension: The West Birmingham Malignant Hypertension Register. *J Hum Hypertens* **19(1):**69–75.
Potter JF, Robinson TG, Ford GA *et al.* (2009) Controlling hypertension and hypotension immediately post-stroke (CHHIPS): a randomised, placebo-controlled, double-blind pilot trial. *Lancet Neurol* **8(1):**48–56.
Ram CV (2006) Review of resistant hypertension. *Curr Hypertens Rep* **8(5):**398–402.
Ram CV, Silverstein RL (2009) Treatment of hypertensive urgencies and emergencies. *Curr Hypertens Rep* **11(5):**307–314.
Schulz V (1984) Clinical pharmacokinetics of nitroprusside, cyanide, thiosulphate and thiocyanate. *Clin Pharmacokinet* **9(3):**239–251.
Silverstein RL, Ram CV (2008) Resistant hypertension. *Prim Care* **35(3):**501–513, vii.
Strandgaard S, Paulson OB (1989) Cerebral blood flow and its pathophysiology in hypertension. *Am J Hypertens* **2(6 Pt 1):**486–492.
Tuncel M, Ram VC (2003) Hypertensive emergencies. Etiology and management. *Am J Cardiovasc Drugs* **3(1):**21–31.
Varon J (2008) Treatment of acute severe hypertension: current and newer agents. *Drugs* **68(3):**283–297.
Vaughan CJ, Delanty N (2000) Hypertensive emergencies. *Lancet* **356(9227):**411–417.
Zeller KR, Von Kuhnert L, Matthews C (1989) Rapid reduction of severe asymptomatic hypertension. A prospective, controlled trial. *Arch Intern Med* **149(10):**2186–2189.

Chapter 7

Abalos, E, Duley L, Steyn DW *et al.* (2007) Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. *Cochrane Database Syst Rev* **1:**CD002252.
Allen C, Glasziou P, Del Mar C (1999) Bed rest: a potentially harmful treatment needing more careful evaluation. *Lancet* **354(9186):**1229–1233.
Atallah AN, Hofmeyr GJ, Duley L (2000) Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. *Cochrane Database Syst Rev* **3:**CD001059.
Clausen T, Djurovic S, Brosstad FR *et al.* (2000) Altered circulating levels of adhesion molecules at 18 weeks gestation among women with eventual preeclampsia: indicators of disturbed placentation in absence of evidence of endothelial dysfunction? *Am J Obstet Gynecol* **182(2):**321–325.
Cooper WO, Hernandez-Diaz S, Arbogast PG *et al.* (2006) Major congenital malformations after first-trimester exposure to ACE inhibitors. *N Engl J Med* **354(23):**2443–2451.
Duckitt K, Harrington D (2005) Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. *BMJ* **330(7491):**565.
Duley L, Henderson-Smart D, Knight M *et al.* (2001) Antiplatelet drugs for prevention of pre-eclampsia and its consequences: systematic review. *BMJ* **322(7282):**329–333.
Epstein FH (1996) Pregnancy and renal disease. *N Engl J Med* **335(4):**277–278.
Ferrer RL, Sibai BM, Mulrow CD *et al.* (2000) Management of mild chronic hypertension during pregnancy: a review. *Obstet Gynecol* **96(5, Part 2):**849–860.
Gilbert JS, Ryan MJ, LaMarca BB *et al.* (2008) Pathophysiology of hypertension during preeclampsia: linking placental ischemia with endothelial dysfunction. *Am J Physiol Heart Circ Physiol* **294(2):**H541–550.
Gilbert WM, Young AL, Danielsen B (2007) Pregnancy outcomes in women with chronic hypertension: a population-based study. *J Reprod Med* **52(11):**1046–1051.
Kaplan NM (2002) *Kaplan's Clinical Hypertension*, 8th edn. Lippincott Williams & Wilkins, Philadelphia.
Loke YW, King A (2000) Immunology of implantation. *Baillières Best Pract Res Clin Obstet Gynaecol* **14(5):**827–837.
Makris A, Thornton C, Hennessy A (2004) Postpartum hypertension and nonsteroidal analgesia. *Am J Obstet Gynecol* **190(2):**577–578.
Matsuo K, Kooshesh S, Dinc M *et al.* (2007) Late postpartum eclampsia: report of two cases managed by uterine curettage and review of the literature. *Am J Perinatol* **24(4):**257–266.
Moore-Maxwell CA, Robboy SJ (2004) Placental site trophoblastic tumor arising from antecedent molar pregnancy. *Gynecol Oncol* **92(2):**708–712.
Redman CW, Sacks GP, Sargent IL (1999) Preeclampsia: an excessive maternal inflammatory response to pregnancy. *Am J Obstet Gynecol* **180(2, Part 2):**499–506.
Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy (2000) *Am J Obstet Gynecol* **183(1):**S1–S22.

Sibai BM (2002) Chronic hypertension in pregnancy. *Obstet Gynecol* **100(2):**369–377.
Widmer M, Villar J, Benigni A *et al.* (2007) Mapping the theories of preeclampsia and the role of angiogenic factors: a systematic review. *Obstet Gynecol* **109(1):**168–180.
Xiong X, Fraser WD, Demianczuk NN (2002) History of abortion, preterm, term birth, and risk of preeclampsia: a population-based study. *Am J Obstet Gynecol* **187(4):**1013–1018.

Chapter 8

Anderson S (1989) Progression of chronic renal disease: role of systemic and glomerular hypertension. *Am J Kidney Dis* **13(6 Suppl 1):**8–12.
Anderson S, Brenner BM (1989) Progressive renal disease: a disorder of adaptation. *Q J Med* **70(263):**185–189.
Bakris GL, Williams M, Dwiorkin L *et al.* (2000) Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. *Am J Kidney Dis* **36(3):**646–661.
Barri YM (2008) Hypertension and kidney disease: a deadly connection. *Current Hypertens Rep* **10(1):**39–45.
Brater DC (1988) Use of diuretics in chronic renal insufficiency and nephrotic syndrome. *Semin Nephrol* **8(4):**333–341.
Campese VM (2000) Neurogenic factors and hypertension in renal disease. *Kidney Int Suppl* **75:**S2–6.
Cooper ME (1998) Pathogenesis, prevention, and treatment of diabetic nephropathy. *Lancet* **352(9123):**213–219.
Coresh J, Astor BC, Greene T *et al.* (2003) Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis* **41(2003):**1–12.
Cowley AW, Skelton MM Jnr., Papanek PE *et al.* (1994) Hypertension induced by high salt intake in absence of volume retention in reduced renal mass rats. *Am J Physiol* **267(5 Pt 2):**H1707–1712.
Grekas D, Bamichas G, Bacharaki D *et al.* (2000) Hypertension in chronic hemodialysis patients: current view on pathophysiology and treatment. *Clin Nephrol* **53:**164–168.
Guidi E, Cozzi MG, Minetti EE *et al.* (2001) Effect of familial hypertension on glomerular hemodynamics and tubulo-glomerular feedback after uninephrectomy. *Am J Hypertens* **14(2):**121–128.
Klag MJ, Whelton PK, Perneger TV (1996) Analgesics and chronic renal disease. *Curr Opin Nephrol Hypertens* **5(3):**236–241.
Kloke HJ, Branten AJ, Huysmans FT *et al.* (1998) Antihypertensive treatment of patients with proteinuric renal diseases: risks or benefits of calcium channel blockers? *Kidney Int* **53(6):**1559–1573.
Lazarus JM, Bourgoignie J, Buckalew VM *et al.* (1997) Achievement and safety of a low blood pressure goal in chronic renal disease. The Modification of Diet in Renal Disease Study Group. *Hypertension* **29(2):**641–650.
Levey AS, Coresh J, Balk E *et al.* (2003) National Kidney Foundation Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. *Ann Intern Med* **139(2):**137–147.
Levin A, Hemmelgarn B, Culleton B *et al.* (2008) Guidelines for the management of chronic kidney disease. *CMAJ* **179(11):**1154–1162.
Lewis EJ L, Hunsicker G, Rodby RA (2001) A clinical trial in type 2 diabetic nephropathy. *Am J Kidney Dis* **38(4 Suppl 1):**S191–194.
Marcantoni C, Jafar TH, Oldrizzi L *et al.* (2000) The role of systemic hypertension in the progression of nondiabetic renal disease. *Kidney Int Suppl* **75:**S44–48.
Merkus MP, Jager KJ, Dekker FW *et al.* (2000) Predictors of poor outcome in chronic dialysis patients: The Netherlands Cooperative Study on the Adequacy of Dialysis. The Necosad Study Group. *Am J Kidney Dis* **35(1):**69–79.
Palmer BF (2001) Impaired renal autoregulation: implications for the genesis of hypertension and hypertension-induced renal injury. *Am J Med Sci* **321(6):**388–400.
Parving HH, LehnertJ, Brochner-Mortensen J *et al.* (2001) The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* **345(12):**870–878.
Phillips AO (2000) Diabetic nephropathy – where next? *QJM* **93(10):**643–646.
Pieratos A, Ouwendyk M, Francoeur R *et al.* (1998) Nocturnal hemodialysis: three-year experience. *J Am Soc Nephrol* **9(5):**859–868.

Rocco MV, Yan G, Heyka RJ *et al.* (2001) Risk factors for hypertension in chronic hemodialysis patients: baseline data from the Hemo Study. *Am J Nephrol* **21(4):**280–288.
Ruggenenti P, Perna A, Gherardi G *et al.* (2000) Chronic proteinuric nephropathies: outcomes and response to treatment in a prospective cohort of 352 patients with different patterns of renal injury. *Am J Kidney Dis* **35(6):**1155–1165.
Ruggenenti P, Perna A, Lesti M *et al.* (2000) Pretreatment blood pressure reliably predicts progression of chronic nephropathies. Gisen Group. *Kidney Int* **58(5):**2093–2101.
Schultz CJ, Neil HA, Dalton RN *et al.* (2000) Risk of nephropathy can be detected before the onset of microalbuminuria during the early years after diagnosis of type 1 diabetes. *Diabetes Care* **23(12):** 1811–1815.
Tolins JP, Raij L (1991) Antihypertensive therapy and the progression of chronic renal disease. Are there renoprotective drugs? *Semin Nephrol* **11(5):**538–548.
Uhlig K, Macleod A, Craig J *et al.* (2006) Grading evidence and recommendations for clinical practice guidelines in nephrology. A position statement from Kidney Disease: Improving Global Outcomes (Kdigo). *Kidney Int* **70(12):**2058–2065.
White KE, Bilous RW (2000) Type 2 diabetic patients with nephropathy show structural-functional relationships that are similar to type 1 disease. *J Am Soc Nephrol* **11(9):**1667–73.

Chapter 9

Alcazar JM, Rodicio JL (2000) Ischemic nephropathy: clinical characteristics and treatment. *Am J Kidney Dis* **36(5):**883–893.
Alcazar JM, Rodicio JL (2000) Hypertension and ischemic nephropathy. *Curr Hypertens Rep* **2(4):**343–344.
Balk E, Raman G, Chung M *et al.* (2006) Effectiveness of management strategies for renal artery stenosis: a systematic review. *Ann Intern Med* **145(12):**901–912.
Cheung CM, Wright JR, Shurrab AE *et al.* (2002) Epidemiology of renal dysfunction and patient outcome in atherosclerotic renal artery occlusion. *J Am Soc Nephrol* **13(1):**149–157.
Cooper CJ, Murphy TP (2007) Is renal artery stenting the correct treatment of renal artery stenosis? The case for renal artery stenting for treatment of renal artery stenosis. *Circulation* **115(2):**263–269, discussion 70.
Greco BA, Breyer JA (1997) Atherosclerotic ischemic renal disease. *Am J Kidney Dis* **29(2):**167–187.
Hansen KJ, Cherr GS, Craven TE *et al.* (2000) Management of ischemic nephropathy: dialysis-free survival after surgical repair. *J Vasc Surg* **32(3):**472–481, discussion 81–82.
Hirsch AT, Haskal ZJ, Hertzer NR *et al.* (2006) ACC/AHA Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Associations for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients with Peripheral Arterial Disease). Summary of recommendations. *J Vasc Interv Radiol* **17(9):**1383–1397, quiz 98.
Horvath JS, Waugh RC, Tiller DJ *et al.* (1982) The detection of renovascular hypertension: a study of 490 patients by renal angiography. *Q J Med* **51(202):**139–146.
Korsakas S, Mohaupt MG, Dinkel HP *et al.* (2004) Delay of dialysis in end-stage renal failure: prospective study on percutaneous renal artery interventions. *Kidney Int* **65(1):**251–258.
Leertouwer T C, Gussenhoven EJ, Bosch JL *et al.* (2000) Stent placement for renal arterial stenosis: where do we stand? A meta-analysis. *Radiology* **216(1):**78–85.
Mann SJ, Pickering TG (1992) Detection of renovascular yypertension. State of the art: 1992. *Ann Intern Med* **117(10):**845–853.
Messerli F, Bangalore S, Makani H *et al.* (2011) Flash pulmonary oedema and bilateral renal artery stenosis: the Pickering syndrome. *Eur Heart J* **32(18):**2231–2235.
Muray SM, Martin ML, Amoedo C *et al.* (2002) Rapid decline in renal function reflects reversibility and predicts the outcome after angioplasty in renal artery stenosis. *Am J Kidney Dis* **39(1):**60–66.
Postma CT, Joosten FB, Rosenbusch G *et al.* (1997) Magnetic resonance angiography has a high reliability in the detection of renal artery stenosis. *Am J Hypertens* **10(9 Pt 1):**957–963.
Ram CV (2006) Review of resistant hypertension. *Curr Hypertens Rep* **8(5):**398–402.
Silverstein RL, Ram CV (20080 Resistant hypertension. *Prim Care* **35(3):**501–13, vii.

Tullis MJ, Caps MT, Zierler RE *et al*. (1999) Blood pressure, antihypertensive medication, and atherosclerotic renal artery stenosis. *Am J Kidney Dis* **33(4):**675–681.

Tuttle KR, Chouinard RF, Webber JT *et al*. (1998) Treatment of atherosclerotic ostial renal artery stenosis with the intravascular stent. *Am J Kidney Dis* **32(4):**611–622.

Chapter 10

Anderson GH Jr, Blakeman N, Streeten DH (1994) The effect of age on prevalence of secondary forms of hypertension in 4429 consecutively referred patients. *J Hypertens* **12(5):**609–615.

Blumenfeld JD, Sealey JE, Schlussel Y *et al*. (1994) Diagnosis and treatment of primary hyperaldosteronism. *Ann Intern Med* **121(11):**877–885.

Bravo EL (1994) Primary aldosteronism. Issues in diagnosis and management. *Endocrinol Metab Clin North Am* **23(2):**271–283.

Celen O, O'Brien MJ, Melby JC *et al*. (1996) Factors influencing outcome of surgery for primary aldosteronism. *Arch Surg* **131(6):**646–650.

Duncan JL 3rd, Fuhrman GM, Bolton JS *et al*. (2000) Laparoscopic adrenalectomy is superior to an open approach to treat primary hyperaldosteronism. *Am Surg* **66(10):**932–935; discussion 35–36.

Fardella CE, Mosso L, Gomez-Sanckez C *et al*. (2000) Primary hypoaldosteronism in essential hypertensives: prevalence, biochemical profile, and molecular biology. J Clin Endocrinol Metab **85(5):**1836–1837.

Gardner DG, Shoback DM (2011) *Greenspan's Basic and Clinical Endocrinology*, 9th edn. McGraw-Hill Medical, New York.

Ghose RP, Hall PM, Bravo EL (1999) Medical management of aldosterone-producing adenomas. *Ann Intern Med* **131(2):**105–108.

Gill I S (2001) The case for laparoscopic adrenalectomy. *J Urol* **166(2):**429–436.

Gonzalez-Campoy JM, Romero JC, Knox FG (1989) Escape from the sodium-retaining effects of mineralocorticoids: role of ANF and intrarenal hormone systems. *Kidney Int* **35(3):**767–777.

Hall JE, Granger JP, Smith MJ Jnr. *et al*. (1984) Role of renal hemodynamics and arterial pressure in aldosterone 'escape'. *Hypertension* **6(2 Pt 2):**1183–1192.

Kaplan NM(2002) *Kaplan's Clinical Hypertension*, 8th edn. Lippincott Williams & Wilkins, Philadelphia:.

Loh KC, Koay ES, Khaw MC *et al*. (2000) Prevalence of primary aldosteronism among Asian hypertensive patients in Singapore. *J Clin Endocrinol Metab* **85(8):**2854–2859.

Mattsson C, Young WF Jr. (2006) Primary aldosteronism: diagnostic and treatment strategies. *Nat Clin Pract Nephrol* **2(4):**198–208; quiz, 1 p following 230.

McKenzie TJ, Lillegard JB, Young WF Jr. *et al*. (2009) Aldosteronomas – state of the art. *Surg Clin North Am* **89(5):**1241–1253.

Meyer A, Brabant G, Behrend M (2005) Long-term follow-up after adrenalectomy for primary aldosteronism. *World J Surg* **29(2):**155–159.

Napoli C, Di Gregorio F, Leccese M *et al*. (1999) Evidence of exercise-induced myocardial ischemia in patients with primary aldosteronism: The Cross-Sectional Primary Aldosteronism and Heart Italian Multicenter Study. *J Investig Med* **47(5):**212–221.

Nishimura M, Uzu T, Fujii T *et al*. (1999) Cardiovascular complications in patients with primary aldosteronism. *Am J Kidney Dis* **33(2):**261–266.

Rossi GP, Sacchetto A, Chiesura-Corona M *et al*. (2001) Identification of the etiology of primary aldosteronism with adrenal vein sampling in p atients with equivocal computed tomography and magnetic resonance findings: results in 104 consecutive cases. *J Clin Endocrinol Metab* **86(3):**1083–1090.

Sawka AM, Young WF, Thompson GB *et al*. (2001) Primary aldosteronism: factors associated with normalization of blood pressure after surgery. *Ann Intern Med* **135(4):**258–261.

Stewart PM (1999) Mineralocorticoid hypertension. *Lancet* **353(9161):**1341–1347.

Suzuki Y, Nakada T, Izumi T *et al*. (1999) Primary aldosteronism due to aldosterone producing adenoma without hypertension. *J Urol* **161(4):**1272.

Sywak M, Pasieka JL (2002) Long-term follow-up and cost benefit of adrenalectomy in patients with primary hyperaldosteronism. *Br J Surg* **89(12):**1587–1593.

Torres VE, Young WF Jnr., Offord KP *et al*. (1990) Association of hypokalemia, aldosteronism, and renal cysts. *N Engl J Med* **322(6):**345–351.

Wang XY, Masilamani S, Nielsen J *et al*. (2001) The renal thiazide-sensitive Na-Cl cotransporter as mediator of the aldosterone-escape phenomenon. *J Clin Invest* **108(2):**215–222.

Wu F, Bagg W, Drury PL (2000) Progression to accelerated hypertension in untreated primary aldosteronism. *Aust N Z J Med* **30(1):**91.
Young WF Jr. (2003) Minireview: primary aldosteronism – changing concepts in diagnosis and treatment. *Endocrinology* **144(6):**2208–2213.

Chapter 11

Beard CM, Sheps SG, Kurland LT *et al.* (1983) Occurrence of pheochromocytoma in Rochester, Minnesota, 1950 through 1979. *Mayo Clin Proc* **58(12):**802–804.
Bravo EL (1991) Pheochromocytoma: new concepts and future trends. *Kidney Int* **40(3):**544–556.
Bravo EL (1994) Evolving concepts in the pathophysiology, diagnosis, and treatment of pheochromocytoma. *Endocr Rev* **15(3):**356–368.
Colson P, Ryckwaert F, Ribstein J *et al.* (1998) Haemodynamic heterogeneity and treatment with the calcium channel blocker nicardipine during phaeochromocytoma surgery. *Acta Anaesthesiol Scand* **42(9):**1114–1119.
Eisenhofer G, Huynh TT, Hiroi M *et al.* (2001) Understanding catecholamine metabolism as a guide to the biochemical diagnosis of pheochromocytoma. *Rev Endocr Metab Disord* **2(3):**297–311.
Eisenhofer G, Walther M, Keiser HR *et al.* (2000) Plasma metanephrines: a novel and cost-effective test for pheochromocytoma. *Braz J Med Biol Res* **33(10):**1157–1169.
Gardner DG, Shoback DM (2011) *Greenspan's Basic and Clinical Endocrinology*, 9th edn. McGraw-Hill Medical, New York.
Guller U, Turek J, Eubanks S *et al.* (20060 Detecting pheochromocytoma: defining the most sensitive test. *Ann Surg* **243(1):**102–107.
Kaplan NM (2002) *Kaplan's Clinical Hypertension*, 8th edn. Lippincott Williams & Wilkins, Philadelphia.
Kudva YC, Sawka AM, Young WF Jr. (2003) Clinical review 164: the laboratory diagnosis of adrenal pheochromocytoma: the Mayo Clinic experience. *J Clin Endocrinol Metab* **88(10):**4533–4539.
Lebuffe G, Dosseh ED, Tek G *et al.* (2005) The effect of calcium channel blockers on outcome following the surgical treatment of phaeochromocytomas and paragangliomas. *Anaesthesia* **60(5):**439–444.
Lenders JW, Keiser HR, Goldstein DS *et al.* (1995) Plasma metanephrines in the diagnosis of pheochromocytoma. *Ann Intern Med* **123(2):**101–109.
Najm PS, Ruby EB, de Papp AE (19970 A 37-year-old female with a shoulder mass and hypertensive crisis. *J Clin Endocrinol Metab* **82(12):**3972–3975.
Pacak K, Goldstein DS, Doppman JL *et al.* (2001) A 'Pheo' lurks: novel approaches for locating occult pheochromocytoma. *J Clin Endocrinol Metab* **86(8):**3641–3646.
Pacak K, Linehan WM, Eisenhofer G *et al.* (2001) Recent Advances in Genetics, Diagnosis, Localization, and Treatment of Pheochromocytoma. *Ann Intern Med* **134(4):**315–329.
Plouin PF, Duclos JM, Soppelsa F *et al.* (2001) Factors associated with perioperative morbidity and mortality in patients with pheochromocytoma: analysis of 165 operations at a single center. *J Clin Endocrinol Metab* **86(4):**1480–1486.
Prys-Roberts C (2000) Phaeochromocytoma: recent progress in its management. *Br J Anaesth* **85(1):**44–57.
Sawka AM, Jaeschke R, Singh RJ *et al.* (2003) A comparison of biochemical tests for pheochromocytoma: measurement of fractionated plasma metanephrines compared with the combination of 24-hour urinary metanephrines and catecholamines. *J Clin Endocrinol Metab* **88(2):**553–558.
Sawka AM, Prebtani AP, Thabane L *et al.* (2004) A systematic review of the literature examining the diagnostic efficacy of measurement of fractionated plasma free metanephrines in the biochemical diagnosis of pheochromocytoma. *BMC Endocr Disord* **4(1):**2.
Tauzin-Fin P, Sesay M, Gosse P *et al.* (2004) Effects of perioperative alpha1 block on haemodynamic control during laparoscopic surgery for phaeochromocytoma. *Br J Anaesth* **92(4):**512–517.
Taylor RL, Singh RJ (2002) Validation of liquid chromatography-tandem mass spectrometry method for analysis of urinary conjugated metanephrine and normetanephrine for screening of pheochromocytoma. *Clin Chem* **48(3):**533–539.
Ulchaker JC, Goldfarb DA, Bravo EL *et al.* (1999) Successful outcomes in pheochromocytoma surgery in the modern era. *J Urol* **161(3):**764–767.
Witteles RM, Kaplan EL, Roizen MF (2000) Sensitivity of diagnostic and localization tests for pheochromocytoma in clinical practice. *Arch Intern Med* **160(16):**2521–2524.

MEDICINE

Hypertension

A CLINICAL GUIDE

Hypertension has become a major public health hazard not only in industrialized nations, but also in emerging economies. Early detection combined with effective treatment is imperative to reduce the risk of patients developing premature cardiovascular disease and accelerated atherosclerosis. *Hypertension: A Clinical Guide* provides a clear, concise resource for everyday use by medical professionals confronting hypertension. This book is of practical value to primary care doctors around the world who deal with patients with hypertension every day.

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Taylor & Francis Group
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K22077
ISBN-13: 978-1-84076-201-3
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