REVIEW ARTICLE

Drugs 2000; 59 Suppl. 2: 1-12
0012-6667/00/0002-0001/$25.00/0

Pathoaetiology, Epidemiology and Diagnosis of Hypertension

Morris J. Brown and *Stephen Haydock*

Clinical Pharmacology Unit, Addenbrookes Hospital, University of Cambridge, Cambridge, England

Abstract

Hypertension is currently defined in terms of levels of blood pressure associated with increased cardiovascular risk. A cut-off of 140/90mm Hg is accepted as a threshold level above which treatment should at least be considered. This would give a prevalence of hypertension of about 20% of the adult population in most developed countries. Hypertension is associated with increased risk of stroke, myocardial infarction, atrial fibrillation, heart failure, peripheral vascular disease and renal impairment. Hypertension results from the complex interaction of genetic factors and environmental influences. Many of the genetic factors remain to be discovered, but environmental influences such as salt intake, diet and alcohol form the basis of nonpharmacological methods of blood pressure reduction.

Investigation of the individual hypertensive patient aims to identify possible secondary causes of hypertension and also to assess the individual's overall cardiovascular risk, which determines the need for prompt and aggressive therapy. Cardiovascular risk can be determined from (i) target organ damage to the eyes, heart and kidneys; (ii) other medical conditions associated with increased risk; and (iii) lifestyle factors such as obesity and smoking. Secondary causes of hypertension are individually rare. Screening tests should be initially simple, with more expensive and invasive tests reserved for those in whom a secondary cause is suspected or who have atypical features to their presentation.

The main determinants of blood pressure are cardiac output and peripheral resistance. The typical haemodynamic finding in patients with established hypertension is of normal cardiac output and increased peripheral resistance. Treatment of hypertension should initially use nonpharmacological methods. Selection of initial drug therapy should be based upon the strength of evidence for reduction of cardiovascular mortality in controlled clinical trials, and should also take into account coexisting medical conditions that favour or limit the usefulness of any given drug. Given this approach, it would be reasonable to use a thiazide diuretic and/or a β-blocker as first-line therapy unless there are indications to the contrary. Individual response to given drug classes is highly variable and is related to the underlying variability in the abnormal pathophysiology.

There are data to suggest that the renin-angiotensin system is more important in young patients. The targeting of this system in patients under the age of

50 years with a β-blocker (or ACE inhibitor), and the use of a thiazide diuretic (or calcium antagonist) in patients over 50 years, may enable blood pressure to be controlled more quickly.

1. Classification of Hypertension

The systemic blood pressure in any given population is a continuously distributed variable. This distribution shifts to the right with advancing age, while individual blood pressure readings for members of the population vary according to the time of day, level of physical activity and degree of emotional stress. Therefore, the selection of a single threshold level of blood pressure that separates hypertension and normotension is likely to be misleading. The current definitions and classifications aim to define hypertension in terms of persistently elevated levels of blood pressure that are associated with an increased risk of the recognised complications of hypertension, in particular stroke and coronary artery disease.

The World Health Organization-International Society of Hypertension (WHO-ISH) have recently published Guidelines for the Management of Hypertension.[1] These guidelines now harmonise with those of the US Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VI).[2] Hypertension is defined as a systolic blood pressure (SBP) of 140mm Hg or greater and/or a diastolic blood pressure (DBP) of 90mm Hg or greater in individuals not taking antihypertensive medication. The WHO-ISH classification of blood pressure levels in adults over the age of 18 years is shown in table I.

The current approach to the treatment of hypertension emphasises that the elevated blood pressure be seen in the context of the overall cardiovascular risk of the individual patient. The requirement for antihypertensive therapy is not simply based upon the magnitude of the blood pressure elevation, but must also take into account the presence of coexisting cardiovascular risk factors, related medical conditions and target organ damage. The assessments of overall cardiovascular risk can be made either by consulting tables or by using programs such as that easily downloaded from the British Hypertension Society web site.[3]

2. Epidemiology of Hypertension

2.1 Prevalence of Hypertension

If the WHO-ISH threshold of 140/90mm Hg (or a level requiring antihypertensive drug treatment) is chosen, then approximately 20% of the entire US population are hypertensive, including the majority of those aged over 80 years. A similar overall prevalence is seen in most developed countries. Differences in prevalence are seen between ethnic groups in the US, with hypertension being more common among Blacks than Whites and being associated with a higher mortality.[4] Marked differences in the prevalence of hypertension can be seen among similar populations living in a single country. A 3-fold variation in prevalence was seen in middle-aged men living in 24 towns in England.[5] Most of this variation remained unexplained despite consideration of other demographic variables.

Table I. Classification of blood pressure levels (from World Health Organization-International Society of Hypertension Guidelines, 1999[1])

Category	Blood pressure (mm Hg)	
	systolic	diastolic
Normal	<130	<85
High normal	130-139	85-89
Grade 1 hypertension (mild)	140-159	90-99
subgroup: borderline	140-149	90-99
Grade 2 hypertension (moderate)	160-179	100-109
Grade 3 hypertension (severe)	≥180	≥110
Isolated systolic hypertension	≥140	<90
subgroup: borderline	140-149	<90

2.2 Blood Pressure and Advancing Age

Blood pressure is seen to rise with age in most Western societies. The rate of rise for blood pressure tends to be greater in females than males after the teenage years (boys of 18 years have SBP up to 10mm Hg and DBP up to 5mm Hg higher than girls of the same age), and greater in Blacks than Whites.[6] Blood pressure tends to track over time so that individuals maintain the same overall rank position within the population. A high-normal blood pressure in a young individual can thus be predictive of the development of hypertension later in life.

2.3 Secular Trends in Hypertension

A decline in population blood pressure levels has been seen in a number of Westernised populations. The US National Health Examination Survey data indicate a decline in population blood pressure between 1960 to 1962 and 1976 to 1980. SBP in White males fell from 133 to 129mm Hg.[7] Similar falls were seen in women and across ethnic groups. The effect was particularly marked with increasing age.

2.4 Blood Pressure and Cardiovascular Disease Risk

The treatment of hypertension is aimed at reducing morbidity and mortality from a range of cardiovascular complications. Levels of blood pressure are positively correlated with both cerebral haemorrhage and cerebral infarction. The slope of the association with blood pressure declines with increasing age (although stroke is numerically much more common in the elderly). A reduction in DBP by 5mm Hg lowers the risk of stroke by one-third.[8] No lower level could be identified below which the risk of stroke declined.

Levels of blood pressure are positively and continuously related to the risk of coronary artery death or non-fatal myocardial infarction. The slope of the association is only two-thirds that of stroke. A 5mm Hg reduction in DBP was associated with a one-fifth reduction in the risk of a coronary event.[8] As for stroke, no lower level has been identified below which the risks of myocardial infarction declined.

In the Framingham Study, hypertension conferred a 2- to 6-fold increased risk of the development of heart failure.[9] Hypertension was also found to be the most important single risk factor for the development of atrial fibrillation, conferring a 1.5-fold increased risk in men and a 1.4-fold increased risk in women. Hypertension was thus responsible for 14% of the atrial fibrillation in this population.[10] It was also found to be associated with a 2.5- to 4-fold increased risk of claudication.[11]

The role of hypertension as a primary determinant in the development of renal disease remains unresolved. Few individuals with essential hypertension develop renal failure, but the risk rises in line with the magnitude of blood pressure elevation.[12] Hypertension is associated with a more rapid progression of renal damage regardless of the aetiology.[13]

There may be ethnic differences in the types of complications most likely to result from hypertension. In all populations, it is important to emphasise that prevention of stroke is the major objective, because, of the two most common complications, stroke has the higher relative risk, which also appears to be completely reversed by adequate treatment. In populations where myocardial infarction is more common overall, the attributable risk of myocardial infarction is also higher in hypertensive individuals; however, treatment of risk factors other than hypertension may be necessary to reverse this risk.

3. Pathogenesis and Aetiology of Hypertension

Cardiac output and peripheral vascular resistance are the primary determinants of blood pressure and are regulated by the interaction of many complex physiological systems. Hypertension is the result of abnormalities in these physiological systems that are believed to arise from the interaction of both environmental and genetic factors.

3.1 Genetic Factors in Hypertension

The blood pressure of relatives is more similar than can be attributed to chance. The first degree relatives of hypertensive individuals are more likely to be hypertensive than first degree relatives of normotensive individuals. Adoption and twin studies give heritability estimates for hypertension (that proportion of total variance that can be explained genetically) of between 30 and 60%.[14]

Selective breeding has led to the development of several hypertensive strains of rat. Genetic analyses of these strains have identified a number of genetic loci and individual genes of importance in blood pressure control in this species.[15] The relevance of such animal data to human essential hypertension remains uncertain.

Some phenotypic characteristics show a strong hereditary component and are linked to the development of high blood pressure.[16] Red blood cell sodium-lithium countertransport and urinary kallikrein excretion are among the best characterised. Such linkages are complicated by two considerations. Firstly, they may be secondary phenotypic manifestations of hypertension and, secondly, they may be spurious associations caused by the action of environmental factors on both blood pressure and the intermediate phenotype under study.

Both association and linkage studies[17] have been used in human populations to relate genetic loci or single genes to the risk of hypertension. Such studies have identified a number of potential genes that show variable associations with the hypertensive phenotype. The associations are usually weak, however, and may be found in one study population and not in another.

A small number of hypertensive disorders with a clearly defined genetic defect and mode of inheritance have been identified.[18] These monogenic syndromes are individually too rare to arise in the lifetime practice of most practitioners, but may give insight into how genetic variants can alter blood pressure and determine a patient's best treatment. All the syndromes involve low renin hypertension due to excessive sodium reabsorption, and patients usually present with stroke or severe hypertension under the age of 30 years. These syndromes clearly show the potential importance of salt in causing hypertension; however, their early onset may suggest that salt-sensitivity is of less importance in essential hypertension, whereas low renin hypertension in Caucasian patients aged less than 60 years is the exception. Perhaps lifetime salt intake is more important in essential hypertension, although this remains controversial.

Could essential hypertension include further monogenic syndromes that present later than those described so far? The incidence of hypertension among siblings of 6000 hypertensive patients was determined by Brown.[19] Nearly two-thirds of patients had no known affected siblings, in nearly one-third all siblings were affected and in <10% of patients half the siblings were hypertensive. It was concluded from these unexpected findings that several more such 'monogenic' hypertension disorders might be identified.[19]

Identification of the multiple genes that are believed to contribute to the development of hypertension remains a major goal in hypertension research. The number of genes involved is uncertain and each may make a small contribution to the overall variance in blood pressure in the population, but may be important for an individual. Such work has significant clinical implications. Identification of contributory genes will enable individuals at risk of hypertension to be identified. An understanding of the genetic basis of hypertension (and hence pathophysiology) in any given patient will enable a rational targeted approach to drug therapy for that individual. Such a view is supported by the experience of known monogenic disorders, where single agents targeting an abnormal pathway are more effective (30 to 40% reduction in blood pressure) than in essential hypertension (10% reduction).

3.2 Environmental Factors in Hypertension

Epidemiological associations and intervention studies (in which the relevant environmental influence is altered) have identified a number of dietary

and non-dietary factors that can contribute to the development of hypertension.

Elevated blood pressure is associated with android (upper body) fat distribution in both adults and children. Hypertensive, obese patients placed on a calorie-restricted diet show a fall in SBP of approximately 2 to 3mm Hg and in DBP of 2mm Hg per kg bodyweight loss.[20]

The vegetarian diet is associated with lower levels of blood pressure. When hypertensive individuals consumed a vegetarian diet for 6 weeks, an average fall in SBP of 5mm Hg was seen. This may be due to the relatively higher intake of fibre in vegetarians, rather than differences in dietary fat content.[21]

Populations with a very low sodium intake (<50 mmol/day) had a substantially lower blood pressure than other populations in the INTERSALT study.[22] Sodium restriction was found to give only modest falls in SBP of 4mm Hg and in DBP of 2mm Hg. The response was highly variable between individuals, and elderly patients may be more sensitive.[23] The overall lack of effect reflects the difficulty in reducing sodium intake sufficiently. The average Western sodium intake is 150 mmol/day. Much of the sodium in the Western diet is associated with tinned and processed food. Interventions may reduce the sodium intake to between 70 and 80 mmol/day at best, but diets below 50 mmol/day would be required to substantially lower blood pressure. Many of the benefits of a reduced sodium intake could be due to the reciprocal increase in potassium intake that accompanies diets restricted in sodium. A weak negative association exists between blood pressure and potassium intake. On average, increasing the potassium intake by 80 mmol/day lowers SBP by 5.9mm Hg and DBP by 3.4mm Hg.[24] Such an increase requires oral potassium supplements and is probably only useful in individuals with obvious potassium depletion.

Evidence linking calcium intake and blood pressure is conflicting. The balance of epidemiological data is in favour of a weak negative association.[25] Intervention studies have not supported an important role for calcium.[26] A weak negative association with magnesium intake is seen in epidemiological studies.[27] There are insufficient data to support a hypotensive action of magnesium supplementation, but supplementation could be beneficial in individuals with demonstrated magnesium deficiency.

Epidemiological data support a positive association between blood pressure and alcohol intake. This effect is particularly marked at a consumption in excess of 6 units daily. Blood pressure falls on reduction of alcohol intake and can be an effective approach in heavy drinkers.[28]

Individuals in Western society are becoming increasingly sedentary. It is now generally accepted that exercise gives protection from cardiovascular mortality. A meta-analysis of intervention studies also suggests that SBP could fall by 11mm Hg and DBP by 6mm Hg in those individuals with systolic pressures greater than 140mm Hg.[29]

Repeated exposure to psychogenic stress has frequently been shown to be related to the development of hypertension. High job strain is associated with a 3.1-fold greater odds ratio for hypertension and an increased left ventricular mass index by echocardiography.[30]

Low birth weight from intra-uterine growth retardation is associated with the subsequent development of hypertension in most surveys. It needs to be explained why this association is not seen in childhood, and is amplified throughout life. One possibility is that growth retardation reduces the number of functioning nephrons present at birth. This cannot be reversed despite excellent postnatal nutrition. The resulting reduction in filtration surface leads to a limitation in the ability to excrete sodium and subsequent development of hypertension.[31] However, the birthweight hypothesis has its critics, and will be difficult to prove. The observation that smaller mothers have higher blood pressure and smaller babies shows the difficulty of unravelling cause and effect.[32]

Caffeine is well known for its sympathomimetic pressor effects. The incidence of hypertension in a 32-year follow-up of 1017 former medical students

was about 3-fold higher in those who drank up to 5 cups of coffee per day compared with non-coffee drinkers.[33] On the other hand, the Multiple Risk Factor Intervention Trial (MRFIT) showed that lower blood pressure was associated with an increasing caffeine intake.[34] Smoking can cause an acute but transient rise in blood pressure.[35] Blood pressure tends to be higher in cold weather,[36] and the prevalence of hypertension may be greater in those living at high altitudes[37] and those exposed to a noisy working environment.[38]

Identification of environmental factors in the development of hypertension has been useful in determining lifestyle modifications that can reduce blood pressure in the clinic as well as the requirements for antihypertensive medication.

4. Investigation of the Hypertensive Patient

The clinical assessment and investigation of the hypertensive patient aim to assess the overall cardiovascular risk for the individual and to exclude a secondary cause of hypertension. Previous intolerance of medication and coexisting medical conditions that could contraindicate the use of certain classes of antihypertensive medication should be documented. The consultation also provides the opportunity to obtain information regarding lifestyle factors, modification of which provides the basis of nonpharmacological approaches to lowering blood pressure.

4.1 Assessment of Cardiovascular Risk

The magnitude of both SBP and DBP are not the only determinants of outcome for the hypertensive patient. Evidence of the following risk factors should be sought by clinical assessment and simple laboratory tests:

- a family history of premature cardiovascular disease
- a high risk socioeconomic group, geographical region and ethnic group
- a sedentary lifestyle
- diabetes
- smoking
- alcoholism
- lipid profile.

The presence of cerebrovascular, cardiac, renal and other vascular disease is associated with a considerably worse outcome and should be documented.

All patients should have a thorough physical examination to determine their physical state of health and to look for clues to an underlying cause of hypertension. A full cardiovascular examination with auscultation is undertaken. The radial and femoral pulses are compared to exclude coarctation of the aorta. The kidneys are carefully palpated and the renal angles auscultated for the bruit suggestive of renal artery stenosis. The presence of target organ damage is sought by clinical examination and noninvasive investigation. Fundoscopy should be undertaken in all patients and the state of the retinal vasculature determined. The presence of arterial narrowing and arterio-venous crossing changes should be documented. Retinal infarction, haemorrhages and papilloedema will only occasionally be seen. Retinal photography may be undertaken.

The blood pressure should be measured seated with the arm at the level of the heart with a device that has validated accuracy and is properly calibrated and maintained. Two measurements should be made at each visit. In cases of uncomplicated mild hypertension, the decision to treat should be based upon the sustained elevation of blood pressure measured at monthly intervals over 4 to 6 months. In more severe hypertension, or hypertension associated with target organ damage, repeated observation before treatment is not necessary or warranted.

Clinical trials that have demonstrated benefit from treating hypertension have used clinic blood pressure readings. There is still debate surrounding the use of ambulatory blood pressure monitoring for the diagnosis of hypertension and the monitoring of its treatment. It can be usefully undertaken in cases with unusual blood pressure variability, treatment-resistant hypertension (>150/90mm Hg on 3 drugs) and in the diagnosis of white coat hypertension. The latter constitutes a group of patients

Table II. Investigation of likely causes of secondary hypertension

Condition	Clinical features	Screening tests	Confirmation	Definitive diagnosis
Renoparenchymal disease	History of reflux; family history of polycystic disease; drugs causing renal disease; history of prostatism; renal masses; chronic urine retention	Raised urea, creatinine; proteinuria; abnormal urine sediment	Renal ultrasound; creatinine clearance and 24-hour protein excretion; isotope renogram	Renal biopsy
Renovascular disease	Abrupt onset <30 or >50 years; severe or resistant hypertension; absence of family history of hypertension; heavy smoking; diabetes; other symptoms of vascular disease; deterioration in renal function with ACE inhibitor; abdominal or other vascular bruits	May be normal; hypokalaemia (secondary hyperaldosteronism); proteinuria; raised urea and creatinine due to bilateral disease (ischaemic nephropathy)	Captopril enhanced renogram	Angiography; MR angiography or spiral CT are increasingly acceptable noninvasive alternatives, where available
Coarctation of aorta	Young age of patient; pain in legs on exercise; cold feet; weak femoral pulses; radiofemoral delay; murmurs over anterior and posterior chest wall	Screening tests normal; clinical features are indication for chest radiograph, which may show rib notching or '3' sign	Echocardiography with colour flow doppler; CT scan	Aortography or MR angiography
Primary hyperaldosteronism	Usually asymptomatic; cramps and fatigue from severe hypokalaemia	Raised sodium, low potassium, raised bicarbonate; in the majority of cases, all these may be normal, and the diagnosis suspected from the combination of high-normal sodium and bicarbonate, plus low-normal potassium	Aldosterone **:** renin ratio >850	Selenium cholesterol radionuclide scan; CT or MRI of adrenals; selective adrenal vein sampling; genetic analysis to exclude corticosteroid-remediable aldosteronism
Phaeochromocytoma	Family history of phaeochromocytoma or associated conditions; headaches, sweating, palpitations, dizzy spells	Abnormal 24-hour VMA collection	Pentolinium or clonidine suppression tests	CT or MRI of adrenals and other chromaffin tissues; MIBG radionuclide imaging; venous sampling
Cushing's syndrome	Cushingoid features of bodyweight gain, striae, etc.	Usually normal	Overnight or low dose dexamethasone suppression test	Corticotropin-independent: CT or MRI of adrenals; corticotropin-independent: CT or MRI of pituitary

CT = computed tomography; **MIBG** = *meta*-iodobenzylguanidine; **MR** = magnetic resonance; **MRI** = magnetic resonance imaging; **VMA** = vanillylmandelic acid.

with consistent hypertension in the clinic and consistent normotension by ambulatory monitoring. It must be appreciated that a difference between clinic and ambulatory pressures is normally seen. This difference is approximately 12/7mm Hg. This difference is reflected in the optimal levels of blood pressure control of less than 130/80mm Hg for non-diabetic hypertensives when assessed by ambulatory monitoring.

Plasma urea and creatinine should be measured in all individuals. Urine should be tested for the presence of protein. Any abnormalities may require further assessment, with estimation of renal function by measurement of creatinine clearance and accurate quantification of 24-hour protein excretion.

The presence of left ventricular hypertrophy (LVH) defines a high risk group of hypertensive patients. Clinical and ECG assessment are insensitive in this regard. Echocardiography is commonly employed to more accurately quantify LVH and assess diastolic dysfunction.

Ultrasound or other radiological evidence of atherosclerotic disease is not routinely sought unless indicated by history (transient ischaemic attacks, claudication etc.) or examination (vascular bruits, reduced pulses). Subsequent radiological investigation is aimed at determining the severity and distribution of disease for the purpose of intervention rather than risk assessment.

4.2 Diagnosis of Secondary Causes of Hypertension

The true frequencies of various secondary causes of hypertension in the general hypertensive population are uncertain, since many of the data relate to populations with severe hypertension or those referred specifically for exclusion of a secondary cause. The overall prevalence of all secondary causes is considered to be no more than 5%. It should be appreciated that, given the low prevalence of all secondary causes of hypertension, a positive screening test is neither proof nor even strong evidence for the existence of the disease. It is thus reasonable to begin investigation with the simplest, cheapest and least invasive tests. Further investigation would be indicated in patients whose clinical assessment or screening tests are indicative of an underlying cause, or who have atypical features associated with their presentation. The latter category might include new onset before the age of 20 years or after the age of 50 years, blood pressure >180/110mm Hg, or marked end-organ damage. Poor response to therapy without evidence of compliance problems is an important reason for returning to consider secondary causes later in the management of the patient.

Most medical textbooks give daunting lists of the potential secondary causes of hypertension. A more useful approach to the aetiology of secondary hypertension is based upon knowing the probability of actually encountering particular conditions in the course of clinical practice and guiding the patient assessment to look specifically for those conditions. The aetiology of secondary hypertension has been addressed in a number of published studies examining the general population or patients referred specifically to a hospital clinic for further evaluation.[39-43] These studies identified renoparenchymal disease, renovascular disease, primary aldosteronism, phaeochromocytoma, Cushing's syndrome, coarctation and drug-induced (the oral contraceptive pill) as the only causes in a total of about 10 000 individuals. It is conceivable that a more exhaustive search may have identified other causes, but the yield is likely to have been low and at the expense of costly and invasive investigation. It is thus reasonable to plan the investigation on the basis of these likely conditions while at the same time always considering the possibility of other potential causes. Table II shows an approach to the diagnosis of secondary hypertension based upon simple screening tests interpreted in the context of features suggestive of an underlying aetiology from the history and examination. It is advocated that the following investigations are routinely performed:

- serum levels of creatinine and electrolytes, including bicarbonate
- urinalysis for cells and protein

Table III. Mechanism of action of the main classes of antihypertensive agents

Class	Example	Principal mechanisms of action
β-Blockers	Atenolol, metoprolol	Reduction in cardiac output; reduction in α-adrenoceptor–mediated arteriolar tone; reduction in β-adrenoceptor–mediated renin release
Thiazide diuretics	Bendrofluazide, hydrochlorothiazide, indapamide (thiazide-related)	Promotion of salt and water excretion; direct arteriolar dilation
α-Blockers	Doxazosin, prazosin	Reduction in α-adrenoceptor–mediated arteriolar tone
ACE inhibitors	Captopril, enalapril, lisinopril, perindopril	Blockade of effects of angiotensin on arteriolar tone, and aldosterone on salt and water retention
Angiotensin antagonists	Candesartan, irbesartan, losartan, valsartan	As for ACE inhibitors but selectively block the AT_1 receptor subtype
Calcium antagonists	Amlodipine, diltiazem, nifedipine, verapamil	Arteriolar dilation
Vasodilators	Hydralazine, minoxidil	Arteriolar dilation
Central acting	Clonidine, methyldopa, moxonidine	Central sympathetic blockade

- 24-hour urine collection for vanillylmandelic acid (VMA) or metanephrines, according to local expertise.

Other investigations of increasing sophistication may be indicated according to the clinical picture and the results of the above studies.

5. Pathophysiological Rationale for Treatment

As previously discussed, cardiac output and peripheral resistance are the primary determinants of the systemic blood pressure. The development and persistence of hypertension are therefore due to abnormalities in the control of either or both of these primary determinants. An increase in cardiac output is seen in some young hypertensive patients and may be involved in the development of hypertension, although the typical haemodynamic finding in patients with established hypertension is one of normal cardiac output and elevated peripheral resistance.[44] Given our current ignorance about the specific causes of hypertension, most of the pharmacological (and nonpharmacological) treatments of hypertension are aimed at reducing peripheral resistance and/or cardiac output through modulation of the physiological regulatory pathways.

5.1 Determinants of Cardiac Output and Peripheral Resistance

An increase in cardiac output can arise from either an increase in myocardial contractility due to neural stimulation of the heart or an increase in preload. Preload is itself dependent upon the level of venous tone and the circulating fluid volume. Peripheral resistance is determined by both functional constriction and structural hypertrophy of the arterial resistance vessels. We are able to manipulate these parameters in the following ways:

- direct inhibition of renal sodium and water retention
- blockage of sympathetic nervous activity, either centrally or peripherally
- inhibition of the renin-angiotensin system, resulting in reduction in arterial tone and blockade of aldosterone-mediated salt and water retention
- arteriolar dilation by direct action on the vessel wall to block smooth muscle contraction.

The current range of antihypertensive medications act through one or more of these systems to effect a fall in blood pressure. This is summarised in table III.

5.2 Selection of Appropriate Drug Therapy

Appropriate drug therapy should be initiated after a trial of, or in addition to, nonpharmaco-

logical methods of blood pressure control. The selection of initial drug therapy is influenced by a number of factors:

- strength of evidence for a reduction in cardiovascular complications
- known tolerability and adverse-effect profile of the different drug classes
- coexisting medical conditions that either favour or limit use of particular drug classes
- cardiovascular risk profile of the individual
- likely response to different drug classes based on age and ethnic group.

The best data available in terms of outcome are still for thiazide diuretics and β-blockers, in that order, although data are accumulating for other drug classes, particularly calcium antagonists and ACE inhibitors. Since it is already clear that blood pressure on treatment is the best predictor of outcome, it is likely that in any individual patient the best treatment is the one that lowers blood pressure the most. Given that hypertension is a heterogeneous disorder with regard to aetiology, it is also to be expected that the individual patient response to different drug classes is also highly variable.[45,46]

This variable response has been studied by Dickerson et al.,[47] who conducted a prospective rotation of 4 major drug classes (ACE inhibitor, β-blocker, calcium antagonist and diuretic) in young hypertensive patients. A significant variability in response was found. In addition, it was discovered that there were correlations between the response to ACE inhibitors and β-blockers and also between the response to diuretics and calcium antagonists. The probable drug response was also related to patient age. Patients under the age of 50 years were more likely to respond to an ACE inhibitor or a β-blocker, whereas patients over the age of 50 years were more likely to respond to the diuretic or calcium antagonist. These findings can be explained by the efficacy of ACE inhibitors and β-blockers in high renin hypertension and the efficacy of diuretics and calcium antagonists in low renin hypertension. Younger patients are more likely to have high renin levels contributing to their hypertension, but this becomes less likely with age.

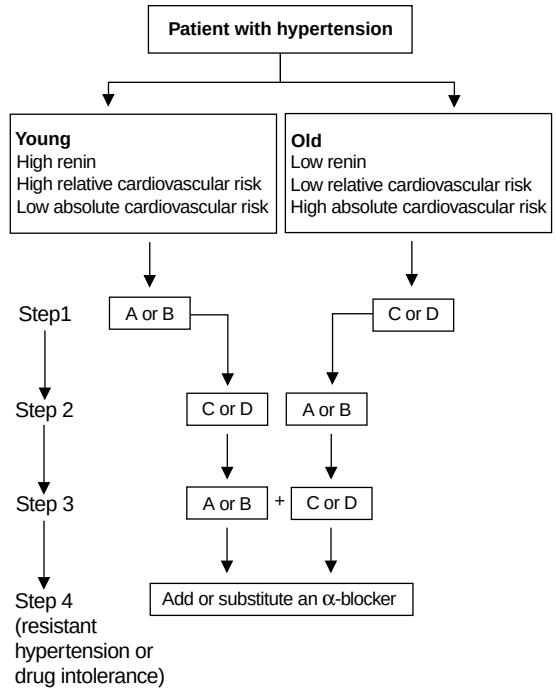

Fig. 1. The Cambridge AB/CD rule for optimisation of antihypertensive treatment. **A** = ACE inhibitor; **B** = β-blocker; **C** = calcium antagonist; **D** = diuretic. Steps 1 and 2 are monotherapy, with the order influenced by the patient's renin status. This is partly determined by the patient's age and ethnic group, permitting initial selection without actual measurement of renin. Steps 3 and 4 are combination therapy. Progress to each step is determined by failure to meet treatment target. Drugs A and B block the renin-angiotensin system, whereas drugs C and D stimulate it.[47]

Use of these data concerning the correlations between drug response and the importance of the renin-angiotensin system in young hypertensive individuals suggests a scheme for drug prescribing in hypertension that aims to optimise the likelihood of obtaining a good response in individual patients. This approach is shown in figure 1. It should be pointed out that the currently available data still support the first-line use of diuretics and β-blockers in the management of hypertension. This scheme suggests that an appropriate first-choice therapy would be a diuretic in the elderly

and a β-blocker in younger patients. More data on the comparison of older and newer drugs will be available in 2000.[48] The current treatment guidelines are based upon clinical trials comparing single therapies with optional additional therapies to reach a goal blood pressure. Most such strategies will therefore result in patients receiving combination therapies rather than single treatment. This results from the fact that for most patients their randomly chosen first drug is unlikely to be that agent to which they have the best response. Any treatment will tend to have a placebo effect and this will be compounded by a tendency for treatment values to regress to the mean. It is thus difficult for the prescribing physician to detect a nil-effect drug. The data from the rotational study may facilitate treatment selection and should be seen as complementing existing treatment guidelines.

6. Conclusions

Hypertension is a common condition associated with serious morbidity and mortality. Treatment by nonpharmacological and pharmacological means should be considered in individuals with a blood pressure greater than 140/90mm Hg. The current best trial evidence favours the use of a thiazide diuretic and/or a β-blocker as a first-choice therapy. The initial selection of these agents can be guided by the age of the patient at presentation: younger patients (under 50 years) respond to a β-blocker (or ACE inhibitor), whereas older patients (over 50 years) respond to a diuretic (or calcium antagonist). Further understanding of the genetic basis of hypertension may enable us to identify the specific abnormalities underlying the rise in blood pressure in any given individual. The future may see us targeting specific abnormal systems in a given individual with specific drug classes.

References

1. WHO-ISH Guidelines Subcommittee. 1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. J Hypertens 1999; 17: 151-83
2. Joint National Committee. The sixth report of the Joint National Committee on detection, evaluation and treatment of high blood pressure (JNC VI). Arch Intern Med 1997; 158: 2413-46
3. Durrington PN. Cardiac risk assessor [computer program]. Available from URL: http://www.hyp.ac.uk/bhs/risk.xls [accessed 1999 Oct 21]
4. Cornoni-Huntley J, LaCroix AZ, Havlik RJ. Race and sex differentials in the impact of hypertension in the United States. The National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. Arch Intern Med 1989; 149 (4): 780-8
5. Shaper AG, Ashby D, Pocock SJ. Blood pressure and hypertension in middle-aged British men. J Hypertens 1988; 6: 367-74
6. Burt VL, Whelton P, Roccella EJ, et al. Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey 1988-1991. Hypertension 1995; 25: 305-13
7. Drizd T, Danenberg AL, Engel A, National Center for Health Statistics. Blood pressure levels in persons 18-74 years of age in 1976-80 and trends in blood pressure from 1960 to 1980 in the United States. Vital and Health Statistics, Series 11, 234, DHHS Pub No (PHS) 86-1864. Washington: US Government Printing Office, 1986
8. MacMahon S, Peto R, Cutler J, et al. Blood pressure, stroke, and coronary heart disease. Pt 1. Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. Lancet 1990; 335: 765-74
9. Kannel WB. Epidemiology and prevention of cardiac failure: Framingham Study insights. Eur Heart J 1987 Sep; 8 Suppl. F: 23-6
10. Kannel WB, Wolf PA, Benjamin EJ, et al. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol 1998; 82 (8A): 2N-9
11. Kannel WB, McGee DL. Update on some epidemiologic features of intermittent claudication: the Framingham Study. J Am Geriatr Soc 1985; 33 (1): 13-8
12. Klag MJ, Whelton PK, Randall BL, et al. End stage renal disease in African-American and White men. JAMA 1991; 265: 599-602
13. Orofino L, Quereda C, Lamas S, et al. Hypertension in primary chronic glomerulonephritis: analysis of 288 biopsied patients. Nephron 1987; 45: 22-6
14. Harrap SB. Hypertension: genes versus environment. Lancet 1994; 344: 169-71
15. Carretero OA, Barman SM, Berecek KH, et al. Major pathogenic factors in hypertension. Hypertension 1991; 18 Suppl. I: 170-3
16. Havlik RJ. Predictors of hypertension. Population studies. Am J Hypertens 1991; 4 (11): 586S-9
17. Corvol P, Persu A, Gimenez-Roqueplo AP, et al. Seven lessons from two candidate genes in human essential hypertension: angiotensinogen and epithelial sodium channel. Hypertension 1999; 33 (6): 1324-31
18. Lifton RP. Molecular genetics of human blood pressure variation. Science 1996; 272: 676-80
19. Brown MJ. The causes of essential hypertension. Br J Clin Pharmacol 1996; 42 (1): 21-7
20. Wadden TA, Foster GD, Letizia KA, et al. A multicenter evaluation of a proprietary weight reduction programme for the treatment of marked obesity. Arch Intern Med 1992; 152: 961-6
21. Margetts BM, Beilin LJ, Armstrong BK, et al. Vegetarian diet in mild hypertension: effects of fat and fibre. Am J Clin Nutr 1998; 48: 801-5

22. Intersalt Cooperative Research Group. Intersalt: an international study of electrolyte excretion on blood pressure. BMJ 1988; 297: 319-28
23. Midgley JP, Matthews AG, Greenwood CMT, et al. Effect of reduced dietary sodium on blood pressure. JAMA 1996; 275: 1590-7
24. Whelton PK, He J, Cutter JA, et al. Effects of oral potassium on blood pressure. JAMA 1997; 277: 1624-32
25. Cappuchio FP, Elliott P, Allender PS, et al. Epidemiologic association between dietary calcium intake and blood pressure: a meta-analysis of published data. Am J Epidemiol 1995; 142: 935-45
26. Bucher HC, Cook RJ, Guyatt GH, et al. Effects of dietary calcium supplementation on blood pressure. A meta-analysis of randomised controlled trials. JAMA 1996; 275: 1016-22
27. Ascherio A, Hennekens C, Willett C, et al. Prospective study of nutritional factors, blood pressure and hypertension among US women. Hypertension 1996; 27: 1065-72
28. Ueshima H, Mikawa K, Baba S, et al. Effect of reduced alcohol consumption on blood pressure in untreated men. Hypertension 1993; 21: 248-52
29. Fayad R. Physical fitness and blood pressure. J Hypertens 1993; 11 Suppl. 5: S47-52
30. Schnall PL, Pieper C, Schwartz JE, et al. The relationship between 'job strain', workplace diastolic blood pressure, and left ventricular mass index. Results of a case-control study. JAMA 1990; 263: 1929-35
31. Mackenzie HS, Brenner BM. Fewer nephrons at birth: a missing link in the aetiology of essential hypertension. Am J Kidney Dis 1995; 26: 91-8
32. Churchill D, Perry IJ, Beevers DG. Ambulatory blood pressure in pregnancy and fetal growth. Lancet 1997; 349: 7-10
33. Mead LA, Wang N-Y, Klag MJ. A prospective study of coffee intake and hypertension: the Johns Hopkins Precursor study [abstract]. J Hypertens 1996; 14: S210
34. Stamler J, Caggiula AW, Gandits GA. Relationship of body mass and alcohol, nutrient, fibre, and caffeine intakes to blood pressure in the special intervention and usual care groups in the Multiple Risk Factor Intervention Trial. Am J Clin Nutr 1997; 65 Suppl.: 338S-65
35. Verdecchia P, Schillaci G, Borgioni C, et al. Cigarette smoking, ambulatory blood pressure and cardiac hypertrophy in essential hypertension. J Hypertens 1995; 13: 1209-15
36. Imai Y, Manakata M, Tsuji I, et al. Seasonal variation in blood pressure in normotensive women studied by home measurements. Clin Sci 1996; 90: 55-60
37. Khalid MEM, Ali ME, Elbagir M, et al. Pattern of blood pressure among high and low altitude residents of Saudi Arabia. J Hum Hypertens 1994; 8: 765-9
38. Wu TN, Ko YC, Chang PY. Study of noise exposure and high blood pressure in shipyard workers. Am J Ind Med 1987; 12 (4): 431-8
39. Gifford RW. Evaluation of the hypertensive patient with emphasis on detecting curable causes. Millbank Mem Fund Q 1969; 335: 97-9
40. Berglund G, Anderson O, Wilhelmsen L. Prevalence of primary and secondary hypertension. BMJ 1976; 2; 554-6
41. Rudnick KV, Sackett DL, Hirst S, et al. Hypertension in a family practice. Can Med Assoc J 1977; 117: 492-7
42. Danielson M, Dammstrom B-G. The prevalence of secondary and curable hypertension. Acta Med Scand 1981; 209: 451-5
43. Sinclair AM, Isles CG, Brown I, et al. Secondary hypertension in a blood pressure clinic. Arch Intern Med 1987; 1289-93
44. Cowley AW. Long-term control of arterial blood pressure. Physiol Rev 1992; 72: 231-300
45. Neaton JD, Grimm Jr RH, Prineas RJ, et al. Treatment of mild hypertension study. Final results. Treatment of Mild Hypertension Study Research Group. JAMA 1993; 270 (6): 713-24
46. Materson BJ, Reda DJ, Cushman WC, et al. Single-drug therapy for hypertension in men. A comparison of six antihypertensive agents with placebo. The Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. N Engl J Med 1993; 328 (13): 914-21
47. Dickerson JEC, Hingorani AD, Ashby MJ, et al. Optimisation of antihypertensive treatment by crossover rotation of four major classes. Lancet 1999; 353: 2008-13
48. Brown MJ, Castaigne A, de Leeuw PW, et al. Study population and treatment titration in the International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT). J Hypertens 1998; 16: 2113-6

Correspondence and reprints: Professor *Morris J. Brown*, Clinical Pharmacology Unit, University of Cambridge, Box 110, Cambridge CB2 2QQ, England.