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Reviews in Medicine

Hypertension

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Introduction

Elevation of the systemic blood pressure remains one of the commonest chronic diseases in westernized populations, and is emerging as a major health problem in the developing world. Despite a large volume of research into both the pathophysiology and the epidemiology of hypertension, the basic underlying cause remains obscure. It is generally held that the elevation of blood pressure is secondary to raised total peripheral resistance, which in turn is caused by narrowing of the lumen of the peripheral arterioles, which are the main resistance vessels.[1] The resultant elevation of pressure in the larger capacitance vessels is then associated with an increased risk of damage to large vessels, mainly in the form of occlusive vascular disease. Thus, hypertension is a major cause of both haemorrhagic and infarctive strokes and is 1 of 3 important risk factors for coronary heart disease. Elevated pressure is closely related to the development of left ventricular hypertrophy and, at extreme levels, to cardiac failure. In addition, hypertension is intimately related to the deterioration of renal function in patients with pre-existing intrinsic renal disease, although there remains some doubt whether hypertension causes renal damage in previously undiseased kidneys.[2] Furthermore, hypertension and its sequelae are major factors in the prognosis of both insulin-dependent and non-insulin-dependent diabetes mellitus.

The as yet unknown aetiology of hypertension is in sharp contrast to the large volume of information on the benefits of reducing blood pressure in terms of the prevention of premature strokes and, to a lesser extent, coronary heart disease. Here at least clinical research into hypertension has provided clear information relevant to practically all branches of medicine. The purpose of this review is mainly to discuss recent advances in the epidemiological and clinical aspects of hypertension with comments on the impact of these new data on the practice of medicine in both a primary and secondary health-care setting. This is preceded, however, by a brief review of some of the most recent research into the elusive basic underlying mechanisms.

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Blood pressure, cardiac output and peripheral resistance

The height of the blood pressure is related to the interplay of the cardiac output and the peripheral vascular resistance. It is known that in established hypertension the cardiac output is normal, so the elevation of pressure is related to the increased resistance to blood flow at a peripheral arteriolar level. It has been postulated that, in the very early stages of the development of raised blood pressure, the cardiac output is raised, possibly due to catecholamine-related left ventricular hyperactivity.[3] In order to maintain normal blood flow, the process of autoregulation leads to peripheral arteriolar narrowing, which in turn causes a rise or further rise in blood pressure. At this stage, for uncertain reasons, the cardiac output then reverts to normal. The proof of this theory must depend on serial measurements of cardiac output over several years and little such research has been conducted.[4]

Arterial narrowing

Despite the above-mentioned hypothesis, most of the basic research has been centred on the development of structural changes in the peripheral arterioles. The early work of Folkow has suggested that the initial phase of this narrowing is caused by vasoconstriction, with increased tone in arteriolar smooth muscle cells.[1] Subsequently more structural or morphological changes develop with medial hypertrophy and vascular remodelling.[5] So what causes this initial vasoconstriction? It is generally held that this is related to neurohumeral factors, which for some reason are hyperactive in people with raised blood pressure. Thus, the autonomic nervous system is known to be active at the postsynaptic alpha 1 receptor and possibly also at

pre-synaptic beta receptors, which may be activated by circulating adrenaline and facilitate noradrenaline release.[6] In addition, there has been considerable interest in the role of circulating vasoconstrictor hormones, including particularly angiotensin II, vasopressin, the prostaglandins and serotonin. However, sensitive assays of these hormones in the circulation have shown either an unconvincing relation with the height of the blood pressure or no relationship and, in the case of the renin angiotensin system, an inverse relationship.[7]

Local vasoconstrictor hormones

Despite the poor relationship between the circulating renin angiotensin system and the increased total peripheral resistance, recent research suggests that many local non-circulating renin systems are operative. The angiotensin converting enzyme (ACE) inhibitors have been shown to be effective antihypertensive agents, even when circulating renin levels are low or even practically unrecordable, as, for example, is seen in anephric patients undergoing chronic dialysis.[8] The concept of local intravascular renin systems is further supported by the finding that, when therapy with the ACE inhibitors is stopped, while plasma levels of the enzyme are rapidly normalized, blood pressure stays down for as long as a few days.[9] Furthermore, when angiotensin II receptors are blocked by saralasin, a synthetic competitive antagonist of angiotensin II, it has been reported that the ACE inhibitors still cause a further fall in blood pressure.[10] The concept of local non-circulating paracrine or autocrine renin angiotensin systems has stimulated a great deal of research and high tissue renin and angiotensin activity have been reported in peripheral vessels, the brain, heart, retina, testis and particularly the efferent arterioles of the kidney.[11-15] As will be discussed later, these local renin systems may be related to vascular damage that is independent of the systemic blood pressure as, for example, in diabetes mellitus and some cases of chronic renal failure.

Endothelin

Another recent development has been the discovery of the new endothelial vasoconstrictor hormone, endothelin. This hormone has now been synthesized and its infusion into humans has been shown to be associated with a sharp rise in blood pressure. Endothelin may well be an important non-circulating vasoconstrictor, although its role in the development of human hypertension is uncertain.[16-17] In normotensive people, positive correlations have been found between endothelin-like immunoreactivity in plasma and mean arterial pressure, although in hypertensive patients a significant negative correlation has been reported.[18]

Vasodilator systems

Peripheral arterioles have a natural constrictor tone related in part to autonomic activity. While some of this vasoconstriction is related to local vasoconstrictor hormones, it is also possible that deficient activity of either circulating or local vasodilator systems is also operative. It has long been known that the circulating kinin system is related to vasodilatation and indeed reduced levels of circulating bradykinin have been reported in systemic hypertension.[19] Furthermore, the ACE inhibitors are known to block the degradation of bradykinin to its inactive metabolites.[20] The dihydryl peptidase enzyme, also known as ACE, does therefore have more than one role.

Endothelial-derived relaxant factor

Since it was first postulated in 1980 by Furchgott and Zawsdzki,[21] endothelial-derived relaxing factor (EDRF) has been found in the arteries and veins of man, where it acts as a vasodilator by diffusing from the endothelium into the vascular smooth muscle.[22] Here it activates soluble granulate cyclase with a resultant increase in the intracellular concentration of cyclic guanosine monophosphate (cGMP), which leads to relaxation of vascular smooth muscle.

Although still controversial, recent research strongly suggests that EDRF is identical to nitric oxide.[23] They appear to share identical biological activity, stability and susceptibility to an inhibitor and to a potentiator. EDRF may play an integral part in the flow-dependent control of vessel diameter. When blood flow increases, the endothelial layer perceives this as an increase in shear stress, which brings about the release of EDRF and consequent vasodilatation. In hypertension, the activity of EDRF is reduced. This may be due to endothelial damage leading to an increase in free radical production, which destroys EDRF.[24] This causes vasoconstriction, which can be reversed by free radical scavengers such as superoxide dismutase.[25] There is also evidence that in atheromatous blood vessels the ability of the damaged endothelium to produce EDRF is greatly reduced.[26] The mechanism for this reduction is not entirely clear; one theory is that it is the lack of muscarinic receptors on the atheromatous endothelium that causes the reduction in acetylcholine-induced release or production of EDRF.

In ischaemic/reperfusion injury studies, there is

evidence that free oxygen radicals, generated by reperfusion after ischaemia, can cause tissue damage. In addition, these radicals can potentiate vasoconstriction, spasm and thrombus formation by destroying EDRF. This would suggest that free radical scavengers may be used to limit the damage caused by reperfusion injury.[27] In this respect, the possible free radical scavenging activity of the sulphydryl (SH) group on the captopril molecule is of some interest.[28] There is, however, as yet no convincing clinical evidence that this drug is any more effective than the other ACE inhibitors in preventing vascular damage.

If EDRF is identical to nitric oxide, this may provide some explanation as to why sodium nitroprusside and the orally active nitrate drugs such as isorbide mononitrate and gliceryl trinitrin have some short-term blood-pressure lowering effects. They may, in fact, be exogenous sources of nitric oxide.

Intracellular sodium and calcium

Epidemiological research, clinical trials and studies of salt-sensitive laboratory animals all support the central role of sodium in the pathogenesis of hypertension. The mechanism by which sodium causes hypertension is not so certain. The original de Wardener hypothesis postulated the existence of a natriuretic hormone that would aid the excretion of sodium by the loop of Henle, but would also by similar mechanisms lead to a rise in intracellular sodium concentration.[29] This prompted a great deal of research into intracellular sodium in hypertension, and it became apparent that many patients with essential hypertension did indeed have high erythrocyte or leucocyte sodium concentrations.[30] It was argued that the raised cell sodium levels in blood cells was a reflection of increased levels in all cells, including the vascular smooth muscle cells. This raised intracellular sodium is maintained by suppression of the sodium pump on cell walls, which is ouabain dependent.[31] A circulating sodium pump inhibitor is clearly necessary if this hypothesis is to be confirmed, and as yet no convincing evidence of such a hormone has been found. It has been suggested that dopamine acts as such a natriuretic hormone, as close correlations have been reported between urine sodium and dopamine concentrations.[32]

An alternative hypothesis as to why there are so many abnormalities of cellular sodium transport in hypertensives and their normotensive relatives has invoked a genetically determined abnormality of the bilipid cell wall of smooth muscle cells.[33] This would move the basic mechanisms of hypertension away from the kidney, usually regarded as the main source of hypertension on the basis of renal cross-transplantation experiments in rats,[34] to a primary abnormality of cell walls. It is likely, however, that a great many differing mechanisms may be required to cause hypertension and it may be naive to hope to define a single cause of essential hypertension, which is so obviously multifactorial. Irving Page was an early proponent of the mosaic theory of hypertension, which drew attention to the many possible mechanisms of hypertension and suggested that all of them may be operative simultaneously.[35]

How then should a raised intracellular sodium concentration cause hypertension? High intracellular concentrations of sodium may lead permissively to a rise in intracellular calcium levels, which in turn could lead to increased contractility of smooth muscle cells.[36] Early work suggested that there was indeed a close correlation between intracellular calcium, in platelets at least, and the height of the blood pressure.[37] However, more recent studies have failed convincingly to reproduce the early reported close correlations.[38] This calcium vasoconstrictor hypothesis does at least provide a theoretical basis for the mode of action of the slow calcium channel blockers such as nifedipine, which, it was postulated, may be the nearest approach to blocking the underlying mechanism of the peripheral arteriolar vasoconstriction.[39] There are many problems with the cellular sodium and calcium data. Firstly, raised intracellular sodium levels and sodium pump inhibition are also found in the normotensive relatives of patients with hypertension.[40] Secondly, the intracellular calcium data are unconvincing.[38] Clearly both have something to do with hypertension but it is difficult to see how they can be directly related to the height of the blood pressure.

Atrial natriuretic peptides

The recent demonstration of a powerful natriuretic and diuretic hormone, secreted mainly from the right atrium, has prompted investigation of these circulating hormones in the pathogenesis of hypertension. Some but not all hypertensives have raised plasma levels of atrial natriuretic peptides compared with normotensives.[41] It is possible that this represents the body's attempts to reduce blood pressure by means of a salt and water diuresis, especially when central vascular volume is increased. Atrial natriuretic peptides may also relax vascular smooth muscle cells and inhibit renin and aldosterone secretion and the symptomatic system.[42,43]

Basic research at a cellular level has therefore advanced over the last 4 years, and both circulating and local vasoconstrictor and vasodilator systems have been described. They provide some explana-

tion as to why the calcium slow channel blockers, the ACE inhibitors and sodium nitroprusside have antihypertensive properties. Also, the hypothesis that hypertension is related to activation of presynaptic beta-receptors may explain how beta-blockers lower blood pressure, independently of their effects on reducing cardiac output, which is, after all, not elevated in established hypertension.

Epidemiological research

Most epidemiological studies strongly suggest that raised blood pressure is related to the interplay of genetic and environmental factors. In support of the genetic hypothesis is clinical experience of the high frequency of positive family histories in hypertensive patients, detailed studies of mono- and dizygotic twins and family blood pressure surveys.[44,45] Furthermore, as stated earlier, inhibition of leucocyte or erythrocyte sodium transport also appears to be genetically determined.[40]

Environmental factors related to the blood pressure of populations have also received much attention. There is no controversy that high body-mass index and a high alcohol intake are related to blood pressure. By contrast, the epidemiological evidence in favour of the salt hypothesis remains controversial.

Insulin resistance, obesity and hypertension

While raised body-mass index and obesity are clearly related to the height of the blood pressure,[46] the mechanisms of this association are still uncertain. The potential confounding effect of the tendency to over-estimate blood pressure in individuals with fat arms does not explain the association. Why then does obesity cause hypertension? It is known that intracellular sodium is raised in some obese subjects, even if blood pressure is not raised, and more recently the hypothesis has been floated that insulin resistance is a common factor in hypertension and obesity as well as diabetes mellitus.[47,48]

Insulin is the most important anabolic and anti-catabolic hormone in the body. It affects many membrane functions, including glucose and amino acid transport, and influences the electrolyte balance across cell membranes. It also acts on intracellular processes such as glycogen synthesis, pyruvate oxidation and lipolysis. In order to exert its effects, insulin binds to specific membrane receptors located on the target tissues – mainly skeletal muscle, liver and adipose tissue. In certain conditions, there is reduced tissue sensitivity to insulin and this is known as insulin resistance. In an insulin-resistant state, plasma glucose is not removed effectively from the circulation and this further stimulates the release of insulin from the islet cells, resulting in hyperinsulinaemia.[49]

The association of hyperinsulinaemia and hypertension was first shown by Welborne *et al.* in 1966[50] and more recently by Modan *et al.*, who studied a population sample of 2,475 Israeli men and women as part of a nationwide longitudinal study.[51] They found a highly significant association between glucose intolerance and hypertension, which held true even when mild hypertension was considered. The rate of glucose intolerance was 27.8% in normotensives, 48.1% in untreated hypertensives and 61.7% in treated hypertensives.

Ferrannini and co-workers, using the euglycaemic insulin clamp technique, have demonstrated peripheral insulin resistance in both obese and non-obese hypertensive patients.[52] They concluded that essential hypertension is an insulin-resistant state in itself and that the site of insulin resistance is in the peripheral tissues, mainly the skeletal muscles, and not in the liver. They also found that the degree of insulin resistance correlated directly with the severity of the hypertension.[48]

Exactly how insulin resistance leads to the development of hypertension is uncertain. However, it is known that, apart from causing glucose uptake by target tissues, insulin has other actions that may result in hypertension. It influences electrolyte balance across cell membranes, which can cause vasoconstriction;[53] also hyperinsulinaemia causes the proximal and distal nephron to absorb sodium, leading to an increase in extracellular volume and cardiac output.[54] Insulin also stimulates the sympathetic nervous system, causing the release of noradrenaline.[55] These multiple effects of insulin, in isolation or combined, could lead to the development of hypertension.

Hypertension, obesity and non-insulin-dependent diabetes mellitus commonly occur in the same individual. Insulin resistance is seen in all 3 of these conditions,[52] but it is not clear whether it is mainly the result of environmental factors, or whether genetic predisposition plays an important role. This is obviously important when considering its possible reversibility by dietary means and the impact of different classes of antihypertensive drugs. The concept of insulin resistance is currently the source of much interest; it is sometimes referred to as Reaven's syndrome or syndrome X.[56] Impaired lipid metabolism, manifested by hypertriglyceridaemia, hypercholesterolaemia and low serum HDL cholesterol levels, is also found in an insulin-resistant state and could predispose to atheroma formation.[56] Insulin may also directly stimulate vascular smooth muscle cell proliferation and plaque formation in arteries[57] With all the associated metabolic changes, it is not surprising, therefore, that subjects with conditions associated with

insulin resistance, for example hypertension, should have an increased risk of adverse cardiovascular events.

It is not clear why insulin resistance occurs in obesity. There may be a common genetic predisposition giving rise to the two conditions, but this is not supported by studies showing an improvement in insulin sensitivity in obese individuals following weight reduction.[58]

Another possibility is that increased levels of free fatty acids seen in obese individuals impair insulin binding and action.[59] Studies have shown that male-type abdominal obesity is associated with more marked insulin resistance than those with the female-type of gluteo-femoral obesity. Abdominal obesity is thus a risk factor for cardiovascular disease and diabetes in both men and women.[60,61] However, available data emphasize the central importance of obesity itself, although fat distribution also plays an important role but only in the presence of obesity.[62]

Non-insulin-dependent diabetes mellitus is associated with an insulin-resistant state and therefore hyperinsulinaemia. It is possible, furthermore, that in insulin-dependent diabetes mellitus the pulsatile nature of insulin therapy could also lead to intermittent 'hyperinsulinaemia' and predispose individuals to cardiovascular disease. This could explain why there is no convincing evidence of a reduction in cardiovascular deaths in diabetes treated with insulin.

Several trials, studying the effect of treating blood pressure in hypertensive subjects, have shown only a disappointing reduction in cardiovascular mortality rates although total mortality and strokes were reduced.[63] This might be because the drugs used in these trials, mainly the thiazides and beta-blockers, are known to induce insulin resistance, so that any benefit from lowering the blood pressure is offset by their metabolic effects. Modern antihypertensive treatment should perhaps aim not just to lower the blood pressure, but also to have a minimum of adverse biochemical and metabolic effects.

The ACE inhibitor captopril and the calcium channel blocker diltiazem have been reported to have no adverse and possibly some beneficial effects on the state of insulin resistance, and other drugs need testing in this respect.[64,65] In the meantime there are strong theoretical grounds for the increasing use of the newer antihypertensive drugs, despite their greater expense.

Alcohol

A similar lack of obvious mechanism is seen with the uncontroversial association between high alcohol intake and raised blood pressure. The possible protective effect of small quantities of alcohol, which was seen with the earlier epidemiological studies, may be spurious.[66,67] It depended on the observation that people who consume no alcohol whatsoever have slightly higher blood pressures than people who consume no more than two drinks or units of alcohol per day. The problem is that the alleged teetotallers represent a very mixed group, including genuine teetotallers, people who have been told to reduce their alcohol intake, people who have deceived their questioners, and patients who are genuinely unwell. Whether or not the relationship between alcohol intake and blood pressure is J-shaped at the bottom end of the distribution, few observers deny that above consumption of 3–4 units of alcohol per day there is a close direct association between alcohol and blood pressure.

The mechanisms are uncertain; alcohol is visibly a vasodilator of some tissue beds and, except in the alcohol-withdrawal syndrome, does not appear to be associated with activation of any of the circulating or neuronal mechanisms of vasoconstriction, except possibly an increased sensitivity to circulating adrenaline levels.[68–70] Animal research suggests that, in some tissues at least, alcohol may be a direct-acting vasoconstrictor.[71,72] There seems little controversy that the pressor effects of alcohol are very reversible. Epidemiological and clinical studies all demonstrate that reducing alcohol intake for as little as a few days is associated with a rapid fall in blood pressure.[73–76]

Salt

Epidemiological evidence in favour of the salt hypothesis was largely derived from comparisons of high and low salt-consuming societies. Thus, the Japanese and the Portuguese have high salt diets and hypertension is common, whereas in primitive tribesmen in South America and subsistence farmers in rural Africa salt intake is very low and hypertension is virtually non-existent.[77] Populations in Europe and the USA have intermediate salt intakes and intermediate blood pressures. There are many objections to this kind of comparison based on an analysis of many different papers in the world literature.[78] The major confounding effects of age, body-mass index, alcohol intake, ambient temperature and the intake of other electrolytes have not been taken into account. In order to overcome some of these objections, the INTERSALT project was conducted.[79] This was a major international epidemiological comparison in which 24 h urine collections were obtained to provide an assessment of dietary salt intake. The project was conducted in 52 populations in 32 countries. Efforts were made to measure all the known

confounding variables, and standardize the techniques of blood pressure measurement and avoid systematic laboratory variations by assaying all the 24 h urine samples in a single, central laboratory.

The results of the INTERSALT project provide comfort both to those who believe and to those who deny the salt hypothesis. There was a weakly significant correlation, when the data from the 52 populations were combined, between median sodium excretion and the systolic blood pressure. However, it was noted that this correlation relied on the inclusion of data from 4 quite distinct low-salt populations from rural Africa and South America. If the statistical analysis was re-run without these 4 low-salt societies, no relation was apparent between salt intake and blood pressure in the remaining 48 centres. The analysis of the relationship between salt excretion and blood pressure in the individual centres did, however, also provide some support for the salt hypothesis. Of the 52 centres, 15 were able to show, within individuals, significant positive relationships between salt intake and blood pressure, and only two reported a negative association. Thus, the INTERSALT project lends some support for the concept that salt intake is related to blood pressure; but the association was weaker than that for blood pressure and body-mass index or alcohol intake.[80,81]

The INTERSALT project did, however, lend support for the role of salt intake in the development of hypertension. Epidemiologists have long appreciated that hypertension was only seen in populations that showed a close association between the height of the blood pressure and advancing age; in populations where blood pressure does not rise with age, hypertension is unheard of. The INTERSALT data showed a highly significant correlation between the median salt intake and the slope of the regression line between pressure rise and advancing age.

Further support for the salt hypothesis derives from the Kenya Luo migration study, where rural Kenyan subsistance farmers were examined before and soon after they migrated to live in urban Nairobi.[82] This migration was accompanied by a sharp rise in blood pressure, which occurred at the same time as a highly significant rise in sodium intake and a fall in potassium intake. This project may provide at least some explanation as to why hypertension is rare in rural Africans, but very common in black populations in African cities, and black people in the UK and the USA.

Salt-depletion studies

The controversy of the epidemiology of the relationship between salt and blood pressure extends into the area of the value of salt depletion in lowering the blood pressure of communities and of hypertensive patients. At a community level, there have been two studies where populations have been subjected to intensive dietary salt restriction advice and compared on a longitudinal basis with control populations that were given no such advice. In the first study in Belgium, there was a statistically significant reduction in sodium excretion in the intervention community but no significant changes were observed in the blood pressure.[83] By sharp contrast, a study from Portugal, a country where salt intake is notoriously high, did show significant falls in mean systolic and diastolic blood pressure in the community subjected to salt restriction advice, compared with the non-intervention community.[84]

These studies are interesting because they were conducted in whole communities, and therefore included normotensives as well as the minority with hypertension. The Portuguese study suggests that salt depletion can indeed reduce the blood pressure in non-hypertensives. It has previously been suggested that salt depletion was only effective in reducing pressure where pressure is high, but this may not be the case.

At a clinical level, against there is a similar degree of inconsistency, although methodological problems render some studies difficult to interpret. The most commonly quoted study by MacGregor *et al.* reported that salt restriction with a reduction of urinary sodium excretion from 180 mmol/day to 80 mmol/day was associated with significant falls in blood pressure.[85] More recently, the same group have conducted a 'dose response curve' in which the degree of salt depletion was found to be related to the achieved reduction in blood pressure.[86]

There are, however, some negative studies, and one of the most important, conducted in South Wales along similar lines to the trial by MacGregor *et al.* showed no fall in pressure in response to salt depletion.[87] However, the blood pressures in this Welsh study were considerably lower than in the hypertensive outpatients studied by MacGregor. If all of the salt depletion studies are combined in an overview, it seems likely that this manoeuvre does reduce blood pressure, because the positive studies are not offset by any reports, in humans at least, that salt depletion raises blood pressure; all studies either show no effect or a modest fall in pressure.[81] The most recent study by Parker *et al.*, conducted among especially recruited volunteers, compared the effects of combined alcohol reduction with salt restriction, and these two manoeuvres were also tested separately.[88] Alcohol restriction with or without concomitant salt restriction caused a fall in blood pressure, whereas salt restriction either alone or with alcohol reduction had no significant effect.

It remains difficult to reconcile the results of all

the salt-depletion studies but variation in salt sensitivity is commonly held to explain some of the variation in response.[89] It is possible that salt sensitivity is partly genetically determined and also that hypertensives are more salt sensitive than normotensives.[90] There is some evidence that hypertensives who have low plasma renin levels, i.e. the elderly, and Afro-Caribbeans, show a bigger response to salt depletion than people with normal or high renin levels.[91,92] There does, however, appear to be no major disadvantage of salt restriction as a method of reducing blood pressure, possibly because the achieved salt intake is not significantly different from that which is already being consumed by many healthy people. However, one recent study from Japan provided suggestive evidence that salt depletion may be associated with a small increase in haematocrit-corrected serum cholesterol levels of a similar order of magnitude to that seen with thiazide diuretics.[93] This study needs to be repeated in other centres if it is to influence clinical practice.

Potassium

There has long been a suspicion that a low potassium intake, either in isolation or in conjuction with a high salt intake, may be related to elevation of the blood pressure as well as to some cardiovascular events, particularly stroke.[94] At an epidemiological level, however, the INTERSALT project failed to confirm that a low potassium intake had a major role in the blood pressure of the 52 communities studies.[79] In the Kenya Luo Migration study, the migration to Nairobi was, however, associated with a fall in potassium intake as well as a rise in sodium intake.[82] There have been several clinical trials of potassium supplementation in the management of mild hypertension, and most have demonstrated significant falls in blood pressure.[95-97] It should be stressed, however, that potassium supplementation with various formulations of potassium chloride is not recommended; but possibly hypertensives who do not have renal failure should be advised to increase their intake of potassium rich foods such as fruit and vegetables, at the same time as restricting their sodium intake.

Calcium

The relationship between calcium intake and blood pressure is similarly controversial. Many epidemiological studies suggest that serum total calcium levels are higher in hypertensives than in normotensives,[98-100] although plasma ionized calcium levels may not be higher.[101] This discrepancy perhaps mirrors the uncertain relationship between blood pressure and intracellular calcium levels.[37,38] These findings contrast with the dietary data from the NHANES study, where calcium intake appeared to be negatively associated with the blood pressure of the populations studied.[102,103] This has prompted McCarron *et al.* to investigate calcium supplementation as a non-pharmacological method of reducing blood pressure.[104] The results of these studies are the source of much debate and clearly further well-conducted trials are required.[105] In the meantime, the calcium hypothesis should not influence clinical practice, particularly as dietary calcium augmentation was in some studies achieved by increasing milk intake, which must therefore be associated with an increase in the intake of animal-based fats.

Stress

The relation between psychosocial stress and blood pressure is equally confused and the many positive studies are largely offset by an equal number of negative results.[106] Intervention studies, where stress management has been used as a method of reducing blood pressure, have provided encouraging results[107,108] but again there are negative studies.[109] It is possible that stress management is effective in reducing blood pressures during clinical consultations but may have no important effects on home blood pressure readings.

Ambulatory blood pressure monitoring

Clinic measurement of blood pressure has been used for many years to diagnose hypertension and to monitor the efficacy of antihypertensive treatment. However, blood pressure is highly variable and has an underlying diurnal pattern.[110,111] The clinic reading can record only a small sample of the daily blood pressure and is influenced by the time of day, the position of the patient at measurement, emotional status and many other stimuli that may cause 'office' or 'white-coat' hypertension.[112,113] The use of ambulatory blood pressure monitoring, in contrast, can provide detailed information on the levels and variability of blood pressure that occur over a 24 h period.[113,114] This can be used to assess the blood pressure load that acts on the heart and the peripheral circulation throughout the day and night.[115] It can also be used for evaluating the efficacy and duration of action of antihypertensive drugs.[116] The data obtained can be used to distinguish between insufficient or incomplete 24 h coverage by the prescribed medication and genuinely resistant hypertension.

Ambulatory blood pressure may be measured continuously by direct intra-arterial measure-

ment,[117] or intermittently by non-invasive techniques using portable recorders that measure the blood pressure by detecting Korotkoff sounds or by oscillometry or by both techniques.[118] The use of invasive techniques is expensive and, in some countries, considered unethical because of the obvious risks associated with its use. It is therefore used only in a few research units and non-invasive ambulatory blood pressure monitoring is more commonly used. A favourable feature of non-invasive ambulatory blood pressure monitoring is that, unlike office measurements, it tends not to trigger an alarm reaction that modifies patients' blood pressure and hence their 24 h blood pressure (BP) profile.[118,119] Its use has demonstrated that between 10% and 21% of patients who are classified as having mild hypertension in the doctor's office have, in fact, normal average daily BP.[120,121]

Many studies have shown that ambulatory blood pressure is superior to office blood pressure in diagnosing hypertension, predicting cardiac end-organ damage and cardiovascular morbidity and mortality.[122-126]

However, despite the enthusiasm for the use of ambulatory monitoring, little is known about what consitutes normal ambulatory BP, and even less information is available to indicate at what level of ambulatory BP antihypertensive treatment should be considered. To answer these questions, Broadhurst *et al.* performed ambulatory intra-arterial blood pressure monitoring on 50 normal volunteers (cuff BP $<140/90$ mmHg) and defined the upper limit of normal daytime BP in both men and women as 150/90 mmHg and the upper limit of mean night time BP as 130/80 mmHg for men and 115/65 mmHg for women.[127] White and Morganroth evaluated 20 normotensive subjects and 20 untreated mild to moderate hypertensive (casual diastolic BP, 95 to 114 mmHg) subjects using non-invasive ambulatory monitors. Their findings suggest that truly hypertensive patients probably have a minimum of 50% of awake readings $>140/90$ mmHg, and the same proportion of the sleep readings BP $>120/80$ mmHg.[116]

Using these latter criteria, the same researchers studied a further 30 untreated mild to moderate hypertensive subjects and found that subjects with more than 40% abnormal ambulatory blood pressures have a likelihood of hypertensive cardiac involvement of 61%, whereas if less than 40% of the BP values were elevated the incidence of an abnormal cardiac test result decreased to less than 17%. The authors concluded that the percentage of elevated BP values that includes both the awake and asleep periods is predictive of cardiac target organ involvement in patients with mild to moderate hypertension, and that patients with mild hypertension who have more than 40% abnormal BP values should strongly be considered for antihypertensive treatment.[126]

Broadhurst *et al.* sounded a cautionary note in a recent editorial review.[128] They pointed out that studies have shown that ambulatory blood pressure monitors are reasonably accurate when used at rest compared to intra-arterial pressure measurements, but only poorly accurate when used during exercise. However, the mean differences in blood pressure using the two methods are random and cancel each other out when pooled. In a clinical setting, even though non-invasive ambulatory blood pressure measurements do not accurately reflect the true ambulatory blood pressure profile of an individual patient, many 'white coat' responders should be correctly identified, allowing a substantial cost saving to be made from decreased medical care and prescription drug costs.

Unfortunately, reliable 24 h ambulatory recording systems are expensive and some do not meet reasonable standards of accuracy and reliability.[129] Further technological developments in this field are needed before this system can be recommended for the routine management of patients.

Left ventricular hypertrophy in hypertension

Left ventricular hypertrophy (LVH), frequently found in hypertensive patients, is now well established as an independent risk factor in cardiovascular morbidity and mortality.[130-132] It is not surprising, therefore, that clinicians and researchers alike now advocate the use of treatments that are known to lead to regression of left ventricular hypertrophy in patients with hypertension. The use of echocardiography allows the reliable assessment of left ventricular mass.[133] However, most clinicians still rely on the electrocardiogram to detect the presence of LVH mainly because echocardiography is expensive and difficult to apply on a mass scale in busy hypertensive clinics. As a test for left ventricular hypertrophy, the electrocardiogram is fairly specific but far less sensitive than echocardiography.[133] It has been shown that left ventricular hypertrophy can be reversed with certain types of antihypertensive therapy.[134-136] Studies in spontaneously hypertensive rats have shown that only drugs that inhibit the sympathetic nervous system or the renin-angiotensin-aldosterone system can reduce left ventricular mass.[137,138] These observations are supported by human clinical studies showing that drugs associated with regression are ACE inhibitors[139,140] and beta-adrenergic blockers,[141] whereas diuretics[142] and direct-acting vasodilating agents are less commonly associated with regression.[143] Results for calcium channel blockers have been rather variable.[144-146] However, it is likely that the most important determinant of regression of LVH is the fall in blood pressure.

Whether the patient's long-term prognosis is improved by regression of LVH is as yet undetermined, but the success of ACE inhibition in reducing deaths in patients with severe cardiac failure is encouraging.[147]

Systolic hypertension

In clinical practice and in all the major morbidity and mortality trials, the criteria for initiating treatment have been based on the height of the diastolic rather than the systolic blood pressure.[63] This concentration on diastolic pressure is perhaps a little surprising in view of the fact that in population surveys the height of the systolic blood pressure has long been known to be a better predictor of morbid or mortal events.[148,149] This may be because with advancing age systolic blood pressure continues to rise steadily, whereas after the age of about 60 years there is a tendency for diastolic pressures to fall.[150] The mechanism of this divergence between systolic and diastolic pressures is uncertain but may be related to a progressive decrease in arterial compliance, with stiffening of large vessels.[151] Thus, one would expect that the height of the systolic pressure would predict death better than diastolic pressure, being almost a reflection of the vascular damage associated with hypertension. When end organ damage at other sites is present, then for a given level of blood pressure the prognosis for the individual is significantly worse. In this respect, isolated systolic hypertension, like the presence of left ventricular hypertrophy, would be expected to carry a poor prognosis.

Despite the well-recognized epidemiological risk it cannot be assumed that reducing the systolic pressure will be beneficial in the same manner as reducing the diastolic pressure.[152] Extrapolation of the relative power of systolic and diastolic pressures to predict events during large-scale randomized trials is not valid, as the criteria for entry into these trials were based on diastolic pressures alone, so that individuals with high systolic but low diastolic pressures were not included.[153] Clinical trials dedicated to investigation of the value of reducing isolated systolic hypertension (SHEP and SYST-EUR) have now been established but results may not become available for some years.[154,155] In the meantime, many clinicians tend to be rather indecisive, although some do opt to start treatment if the systolic blood pressure exceeds 190–200 mmHg. Most patients with isolated systolic hypertension are elderly and there remains some reluctance to prescribe drug therapy in large numbers of fit elderly people unless the benefits of such treatment are proven. Paradoxically, however, the pay-offs from treating diastolic hypertension in the elderly is greater than in younger patients, with a large reduction in incidence of stroke over a few years.[156,157] It remains to be shown whether similar benefits accrue from treating isolated systolic hypertension.

The very elderly

Over the age of about 85 years, the relationship between mortality and the height of the blood pressure becomes less consistent and may be reversed, so that people with higher pressures tend to live longer.[158,159] This may be due to earlier selective mortality of people with high blood pressure, leaving fewer long-standing hypertensives, or it may be due to genuine falls in pressure due to silent or low-grade myocardial ischaemia. Thus, individuals with low blood pressure might have unhealthy hearts and a corresponding poor prognosis.

The value of antihypertensive drugs in the very elderly is the source of some debate. One small study of residents in an old people's home showed no benefits, although the patients included were somewhat selected and may not be typical of old people in general.[160] In a sub-group analysis of the very elderly participants in the EWPHE study there was a suggestion of benefit from drug treatment but no firm conclusions can be drawn.[161] The final publication of the results of the SYST-EUR and SHEP studies[154,155] should provide a great deal of useful information, relevant to a very large number of ambulant elderly people.

The J-shaped curve

While the benefits of drug treatment in patients with diastolic blood pressures exceeding 100 mmHg is now incontrovertible, there remains considerable doubt as to how far blood pressure should be lowered. Early suggestions that hypertensives with low achieved pressures may do badly were largely ignored[162] but more recently 4 large-scale respective studies of the results of treating large numbers of moderate to severe hypertensives have been published. These all appear to demonstrate a slightly higher mortality from coronary heart disease among individuals whose diastolic pressures dropped to below 80 mmHg.[163–166] It should be stressed, however, that these were not randomized controlled trials and that, in those patients whose pressures dropped to between 85 and 100 mmHg, coronary mortality was lower than in less successfully treated cases.

However, the J-shaped relationship between coronary mortality and achieved diastolic pressure is the cause of some concern. This trend was not

seen with systolic blood pressures or with stroke incidence. It has been suggested, therefore, that the J-curve is due to a critical level of blood pressure necessary for diastolic filling of the coronary arteries, particularly in patients who already have some coronary artery disease.[167] No J-curve was observed in patients who had normal electrocardiograms or no heart disease when drug therapy was initiated. Should clinicians be less aggressive when treating patients with pre-existing coronary disease? It is possible that the target diastolic pressures in such cases should be around 90 mmHg, rather than lower. Drug therapy may not, however, be the cause of low diastolic pressure in former hypertensives; if a hypertensive is mysteriously 'cured', a diagnosis of underlying coronary heart disease should be considered. This suggestion is borne out by examining the outlook in untreated elderly hypertensives in the trial by Coope and Warrender,[157,168] where a J-curve was observed in both treated and untreated patients. The absence of a J-curve in participants in the MRC trial of mild hypertension may be related to the very low incidence of coronary heart disease at entry, or throughout the trial, in these younger patients.[169] There may, therefore, be no contest between those studies displaying a J-curve and those that found no such trend. The J-curve may be a feature only of people who have developed coronary heart disease, which has further lowered their pressures, and be unrelated to drug therapy.

Blood pressure and risk

The recent publication of the follow-up of examinees for the MRFIT[170] study and a major overview of all the population studies now provide very accurate information on the relationship between blood pressure, heart attacks and strokes.[171] These confirm that the risk of death in relation to blood pressure extends down to low levels of pressure; with the non-elderly at least, there is no evidence that very low blood pressure in otherwise fit examinees carries a bad prognosis. This therefore negates the earlier suggestion of a 'dog leg' or a J-shaped curve, in populations, between blood pressure and subsequent cardiovascular risk.[172] There has, however, been a recent study that reported that low blood pressures may be associated with an increased morbidity from non-specific non-life-threatening ailments.[173] In the United Kingdom in general, low blood pressures are usually not considered to be serious unless they are associated with autonomic neuropathy or adrenal insufficiency. By contrast, in some continental European countries, hypotension is an important cause of absence from work.

A recent overview analysis of the epidemiology of hypertension has also drawn attention to the synergistic impact of concurrent smoking status and serum cholesterol levels.[171] In many mild hypertensives, the risk of death is not particularly high because of the absence of other risk factors and, conversely, in some cases the severity of the other risk factors is more important than the relative modest blood pressure elevation. This had led many hypertension clinics to develop a more 'multiple risk factor' approach to their patients, with attention being turned to lipids and smoking as well as blood pressure.[174] The initially disappointing results of the formal MRFIT trial dampened enthusiasm for this approach, but the recent publication of the 10.5 year results of that trial does confirm that this manner of managing patients is worthwhile in terms of coronary prevention.[175]

The benefits of blood pressure reduction

When individual mortality/morbidity trials are considered, the results appear a little inconsistent. The recent publication of a meta-analysis of all of the studies with calculations of confidence intervals, comparing the amount of coronary or stroke prevention in relation to the amount of blood pressure reduction, provides a more clear-cut picture.[63] The average blood pressure reduction in these trials was around 5–6 mmHg and, for this reduction, one would expect a 35–40% reduction in strokes. In the trials, the observed stroke reduction was around 42%, thus validating the usefulness of antihypertensive therapy in stroke prevention.

The picture of coronary heart disease was less encouraging. Whereas a 20–25% reduction of coronary heart disease would be expected, the trials achieved only about a 14% reduction. What, therefore, is the reason for the short-fall in the impact of antihypertensive therapy on coronary disease? Part of this may be due to the small but adverse effects that many antihypertensive drugs, and particularly the thiazide diuretics, have on other risk factors including glucose tolerance and plasma lipids, as well as effects of insulin resistance. These adverse effects are the source of some debate, and are probably not large enough to explain all of the short-fall in the benefits of blood pressure reduction. Adverse effects on other risk factors, including clotting factors, are possible but not yet fully investigated. After all, the level of the blood pressure may be a final pathway for an as yet unidentified vascular pathological process, and treating the pressure alone might not be expected to be as useful as treating the underlying mechanism.

There have been many reviews over the years that have questioned whether it matters how blood pressure is reduced.[176] Most have concentrated on

the effects of thiazide diuretics on other cardiovascular risk factors. The recent publication of dose–response data for the use of bendrofluazide suggests that most of its biochemical side effects can be minimized if low doses are used, with no loss of antihypertensive efficacy.[177] No final answer is available but the possible adverse effects of some drugs have led to the search for other methods of reducing blood pressure, particularly with vasodilating agents such as ACE inhibitors and calcium slow channel blockers. These newer agents tend to be expensive[178] and no morbidity/mortality trials are available to show whether they are better than the more conventional drugs such as beta blockers at preventing mortal events. It was hoped that beta receptor blockers would have protective effects against the development of first heart attacks, and the term 'cardioprotection' was commonly used. Randomized controlled trials of beta blockers in the prevention of coronary heart disease in hypertensive patients have provided inconsistent results but a meta-analysis of all such studies suggests overall a very small beneficial effect from beta blockade. In patients who have recovered from a myocardial infarction, beta blockade is still the treatment of first choice,[180] although a recent study has shown that the calcium channel blocker verapamil also reduces the incidence of second cardiovascular events by a similar amount.[181] Previous studies of calcium channel blockade in the secondary prevention of myocardial infarction have been less convincing.[182,183]

It is not the purpose of this review to consider in detail the relative benefits of the different classes of antihypertensive drugs, as no clear consensus has emerged. The lipid neutral effects of the calcium entry blockers and the ACE inhibitors and the possible benefical effects of the new alpha blocking drugs on plasma lipids[184] are all interesting but opinions differ as to whether these should be used as routine first-line drugs or should be used only where other agents are specifically contra-indicated.[176] Some clinicians vigorously defend the older classes of antihypertensive drugs on the grounds that they have been shown to prevent at least some of the complications of the disease and they are, after all, relatively cheap. One recent survey of the relative costs for lives saved by the use of the various types of antihypertensive drugs suggests that expensive drugs are hard to justify.[178] By contrast, analyses of the effects of these drugs on other coronary risk profiles make one prefer to opt for the newer classes of drugs.[185] The argument can be resolved only by long-term comparative trials of all the main classes of drugs in the prevention of heart attacks and stroke. Such trials would be very expensive to conduct, they would take many years to come to fruition and unfortunately none are now under way.

Perhaps the only guidance one can give is that the relative differences in the benefits of the many pharmacological methods of reducing blood pressure are minor compared with the definite benefits of controlling the blood pressure by any means available.

Pregnancy

The mechanism of blood pressure elevation in the various forms of hypertension in pregnancy remains obscure but there appears to be only a modest relationship between mild hypertension in early pregnancy and the more severe form of elevation of blood pressure occurring as part of the syndrome of pre-eclampsia.[186] Only enormous trials involving thousands of mothers could have the power to demonstrate beneficial effects of treating mild hypertension in early or mid-pregnancy, as the perinatal mortality in western countries is now so low and is related to other factors as well as blood pressure. Two trials conducted in early pregnancy suggest that there are no benefits of giving antihypertensive drugs to mild hypertensive mothers if diastolic blood pressures are below 100 mmHg.[187,188] Where antihypertensive drugs are necessary in later pregnancy, the choice remains limited to methyl dopa or the beta blockers including labetolol. The ACE inhibitors are absolutely contra-indicated in pregnancy at any stage and should also not be given to women who are likely to become pregnant.[189] The role of calcium channel blockers is less uncertain, although they have been used as second-line agents in severe hypertension in pregnancy.[190]

Diabetes mellitus

There has been an increasing awareness of the important of elevation of the blood pressure on the complications of both insulin-dependent and non-insulin-dependent diabetes mellitus. Surveys conducted in diabetic clinics reveal that about half of all patients with non-insulin-dependent diabetes mellitus are also hypertensive[191] and that these individuals have a very poor prognosis. At the same time, there has been an increasing disappointment on the value of achieving perfect glycaemic control. As with elevation of the blood pressure, it is probable that the raised blood glucose level in diabetic patients is the final expression of a more fundamental metabolic defect. There is now good evidence that the presence of microalbuminuria with urinary albumin concentrations of below 300 mg/24 h but above 50 mg/24 h ('Albustix negative') is associated with a more rapid rate of deterioration of renal function[192] and progression

to end-stage renal failure. Accurate control of blood pressure appeared to lead to a reduction in microalbuminuria[193] and a possible less rapid decline in renal function.

The work of Zatz *et al.*, who measured intraglomerular pressure in streptozocin-induced diabetes in rats, has led many researchers to attempt to reduce intraglomerular pressure by dilating the post glomerular efferent arterioles with angiotensin converting enzyme inhibitors.[194] It remains to be seen whether the ACE inhibitors bring about a more impressive reduction in urinary albumen excretion than do more conventional antihypertensive agents. Most of the studies have been uncontrolled and conducted on a small scale and, in some, calcium channel blockers have achieved as much, or even more, reduction in microalbuminuria as the ACE inhibitors.[195-197] Long-term prospective randomized controlled trials are urgently necessary not only in diabetic patients with concomitant hypertension but also in normotensive diabetics with increased urinary microalbumin excretion. In the meantime, an increasing number of diabetologists are opting to use the ACE inhibitors when hypertension is present. In terms of glycaemic control and plasma lipids both the thiazides and the beta blockers have possible disadvantages, whereas the calcium channel blockers and the ACE inhibitors appear to be lipid and glucose neutral.

Renal failure

While there remains some doubt whether benign non-malignant essential hypertension is an important cause of renal failure,[2] it is probable that, where renal impairment is present, blood pressure reduction is worthwhile.[198] Initially there was some anxiety about the use of ACE inhibitors in patients with renal failure, on the grounds that reducing blood pressure so effectively might cause a reduction in renal perfusion.[199] Furthermore, there has been some anxiety about the effect of ACE inhibitors in older patients who are smokers and who might have undiagnosed atheromatous renal artery stenosis.[200] In such cases, renal artery occlusion has been reported, as well as a reversible deterioration in renal function.[201,202]

It is possible that on a long-term basis ACE inhibitors may have beneficial effects in patients with renal failure due to renal parenchymal disease but no formal trials are available. Reports of reduction in proteinuria in patients with chronic renal failure with or without the nephrotic syndrome are encouraging, but it is not certain whether these drugs, or for that matter any other class of antihypertensive drugs, have much impact on the otherwise inexorable deterioration to end-stage renal failure.[203]

Conclusions

This review has concentrated on some areas either controversial or where major advances in our understanding have been made. It is not, therefore, able to provide recommendations on how to treat hypertension or how to measure blood pressure accurately. Guidelines on these two important topics have been published by the British Hypertension Society.[204,205]

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