Hypertension update

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Haemodynamics: two types of hypertension?

Some puzzles in the types of presentation and response to treatment of high blood pressure can be rationalised with a conceptual division of the problem into two pathophysiological types. The first and traditionally dominant type is characterised by increased resistance of the small arterioles. It is mostly found in younger patients and is characterised by elevation of both systolic and diastolic BP. The second type is that increasingly recognised in older people and is associated with increased stiffness of the larger arteries. This leads to elevation of systolic pressure, often in isolation or even accompanied by a decrease in diastolic pressure. Of course, both pathophysiological features can co-exist. Awareness of both types and the increasing prevalence of the latter given the ageing population does explain why systolic pressure has replaced diastolic pressure as the most predictive index of risk.

In concert with these concepts is the emergence of interest in inferring central aortic pressure from analysis of the peripheral pulse wave using non-invasive technology – pulse wave tonometry. The pressure wave in the central aorta differs significantly from that in the brachial artery, especially where large arteries are stiffening, and central aortic pressure changes in different ways with varying types of antihypertensive drug therapy. The 'CAFÉ' substudy[1] of the recent ASCOT trial[2] suggested that this may explain some of the better outcomes when a calcium antagonist based therapeutic regimen was compared with one based on a beta blocker; there was a greater fall in central pressure with the former therapy while brachial pressures on the two regimens were similar.

Recognition of the contrasting types of hypertension can also help to guide choice of antihypertensive agents and explain why the older patient may respond better to diuretics and calcium antagonists (CAAs) whereas angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and beta blockers (BBs) prove more useful in the younger patient. Further comments about choice of treatments are given in the section on therapeutics below.

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This dichotomising concept does not undermine the concept of elevated blood pressure being one of a number of risk factors to be managed as part of comprehensive cardiovascular risk reduction rather than a disease process in its own right. Both systolic and diastolic pressure are normally distributed and the gradient of risk increases gradually with elevated levels of pressure, especially systolic. It is important to address other risk factors in the hypertensive patient and, conversely, to treat even mildly elevated blood pressure aggressively when it accompanies other primarily identified conditions (especially diabetes).

What investigations are appropriate for the patient with raised blood pressure?

As with most conditions of varying severity, the intensity of investigation varies with the degree of abnormality. A good history and examination is, as usual, the cornerstone to establish any possible causes or consequences of raised blood pressure *(**tip**: always check leg pulses – it's very embarrassing for an aortic coarctation to be diagnosed after months of frustratingly ineffective treatment).*

Some investigations will be directed at establishing overall cardio-

vascular risk and include fasting glucose and lipids with a glucose tolerance test if fasting glucose is over 5.6 mmol/l. Creatinine (and derived estimated glomerular filtration rate – eGFR) and urinalysis, possibly including estimation of microalbuminuria, will help determine if there has been renal target organ damage requiring a more aggressive approach to therapy. Don't forget electrolytes, a low potassium level should trigger a search for some causes of secondary hypertension (e.g. hyperaldosteronism, Cushing's Syndrome, some renal pathologies). It is also important to establish the baseline level of potassium before administration of any diuretics. A blood count may be useful in identifying any co-morbidities and finding a high level of uric acid may avoid the precipitation of gout with inappropriate diuretic therapy. While an echocardiogram would be ideal, local resources do not allow this for all those with raised blood pressure but an ECG would be a good routine baseline test.

New European guidelines also recommend consideration of carotid ultrasound, ankle-brachial BP index and pulse wave velocity to evaluate vascular target organ effects and associated pathologies. However, their value in asymptomatic patients is doubtful and the more sophisticated tests are not easily available. Additional assessment of blood pressure levels using home or ambulatory methods may be helpful where levels in the surgery are variable, borderline or suspected to be influenced by anxiety of the patient. Do bear in mind that the 'normal range' of readings with such methods is actually lower than that for readings taken in the surgery.

For the younger patient with severe hypertension or the patient highly resistant to simple therapy, further tests for a cause of secondary hypertension can be considered. These include blood levels of renin, aldosterone and corticosteroids, 24-hour urine collection for catecholamines, renal/adrenal ultrasound and computed tomography or magnetic resonance angiography of the renal arteries to look for stenosis.

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New guidelines

Comprehensive new guidelines for managing hypertension have recently been released by the European Society of Hypertension.[3] Highlights of these include advocacy for treating older patients with unequivocal net benefit seen for treatment of those over 60 years. Trials are in progress for the over 80s, preliminary results suggesting treatment reduces morbidity but not mortality. There are hints that cognitive function in the elderly may be better preserved with good blood pressure control.

The particularly high risk of patients with a combination of hypertension and diabetes or renal impairment has been emphasised. Aggressive treatment is therefore advocated here, starting preferentially with an ACEI or ARB. It remains unclear whether acute reduction of blood pressure in those who have just suffered a stroke is beneficial but certainly long-term reduction starting when the situation has stabilised is beneficial, even when the blood pressure is not particularly high. In both of these situations, attention to other risk factors is important too.

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Pharmaceutical treatment

Recent large outcome trials

The very large ALLHAT trial[4] in the USA showed diuretics to be at least as good as (if not better than) CAAs or ACEIs although those on CAAs had fewer strokes. Another large trial published recently – the ASCOT study[2] – showed better outcomes for those preferentially treated with the CAA, amlodipine (+ an ACEI if needed) than those starting with the BB atenolol (+ optional diuretic). Other reviews have also cast doubt on the efficacy of BBs,[5] especially atenolol,[6] although some critics have pointed out that BBs may still be of considerable use in the younger group.[7] These trials and other analyses have also demonstrated that the chronic use of diuretics and beta blockers leads to a higher incidence of glucose intolerance and diabetes, but onward effects of this on overall outcome remain uncertain. A large trial (VALUE[8]) compared amlodipine with the angiotensin receptor blocker, valsartan, and found that blood pressure reduction and outcomes were better with amlodipine. Again, the main conclusion from all comparative trials is that the major determinant of outcome is the degree to which blood pressure is lowered, not the specific choice of agent. In any case, most patients with significantly raised blood pressure should be warned that they will almost certainly need a combination of two or three agents to gain effective control.

General approach

New guidelines are generally abandoning the concept of a fixed stepped approach through a hierarchy of preferred drugs in favour of tailoring choice of treatment to the patient from the beginning. As mentioned

above, the younger patient with elevated diastolic and systolic pressure may respond well to ACE inhibitors or beta blockers whereas the older patient with stiff arteries and isolated systolic hypertension will probably do better on diuretics or CAAs. CAAs have now been fully rehabilitated after safety concerns were raised a decade or so ago.[9] Co-morbidity will often determine the initial therapeutic choice. Examples of conditions predetermining preferred medication are given in Table 1. Most antihypertensive agents will bear only a limited titration before small further gains in blood pressure control are outweighed by a much greater likelihood of side effects. As mentioned in the previous update,[10] ACEI/ARB and BB combination or CAA and diuretic combination is generally less effective than combining one from each pair. A large minority of patients will, however, require a third or fourth drug.

Table 1. Preferred drug group aligned with patient condition (adapted from European Guidelines[3])

Condition	Initial drug preferred
Type of hypertension	
Older patient with systolic HT	D, C
Younger patient with sys and dias HT	A, B
Target organ damage	
Left ventricular hypertrophy	A, C
Renal dysfunction or microalbuminuria	A
Clinical disease	
Stroke	A, D (B, C) etc.
Myocardial infarction	B, A
Angina	B, C
Cardiac failure	D, A, B
Atrial fibrillation	B, C (verapamil* or diltiazem), A
Peripheral vascular disease	C
Renal impairment	A
Other conditions	
Diabetes mellitus	A
Pregnancy	αβ (labetalol), B, C, methyldopa

Key: *HT = hypertension, A = ACE inhibitor/angiotensin receptor blocker, B = Beta Blocker, C = Calcium antagonist, D = diuretic, αβ = alpha-beta blocker*

* The combination of verapamil with a beta blocker should be avoided

Angiotensin receptor blockers and renin inhibitors

One factor influencing a more liberal approach to choice of first drug is that there are now many drugs within each of the above groups that are off-patent so are obtainable relatively cheaply. Exceptions to this are newer drugs such as angiotensin receptor blockers (ARBs) and a new emerging class of direct renin inhibitors. ARBs have been available for a little while and proved particularly useful for patients who respond well to an ACEI but prove intolerant of this due to cough. Because of their expense, PHARMAC limits their use by special authority. Trials have shown by and large that their effects are very similar to those of ACEIs as they act on the same enzyme cascade. Theoretically, they may have additional benefit by blocking angiotensin that is synthesised in the body by non-ACE pathways, but ARBs largely lack the ability that ACEIs have to block bradykininase and have a more selective effect on angiotensin receptors. Bradykinin is a vasodilator and inhibiting its breakdown may contribute to blood pressure reduction. However, it also appears to be the mediator of ACEI-induced cough, an effect which ARBs do not seem to have. Some patients are switched because of a more serious reaction to and ACEI – angio-oedema – but caution is necessary here as there is some cross-reactivity for ARBs.

There may be advantages in some circumstances in combining an ACEI and ARB. Interpreting relevant trials can be blighted by the difficulty of being certain that the same effect seen with the combination could not have been achieved with maximal titration of the ACEI alone.

Other drugs

Outside the major four 'ABCD' categories (lumping both ACEIs and ARBs into the 'A' group) there are some other drugs which are occasionally useful. Alpha blockers are no longer first choice agents as they are less effective than the others, are associated with a slightly higher incidence of heart failure and can cause incontinence in women and postural hypotension when used in high doses. However, they can be useful as alternatives or adjuncts where needed. Labetalol has combined alpha and beta blocking effects and has a particular established role where antihypertensive therapy is required during pregnancy. Methyldopa is still used as a fifth or sixth choice agent (and again in pregnancy) but makes a fair proportion of those who use it drowsy or depressed; twice daily use is adequate, preferably with a larger dose at night. I do not personally recommend clonidine at all given the risk of severe rebound reactions if doses are missed and the frequent

cutaneous reactions to the skin patches sometimes used for its administration.

The new oral direct renin inhibitor, aliskiren, is becoming available in some countries and, although interesting as the first drug in a new class, it does not seem to be producing a major therapeutic revolution in antihypertensive efficacy. It works by inhibiting the rate-limiting step of the renin-angiotensin system reducing the capacity of renin to form angiotensin I. Its place in the armamentarium is yet to be ascertained.

Resistant hypertension

Most practitioners will have patients whose blood pressure appears to be particularly resistant to treatment. In such cases it is important to check methods of blood pressure measurement:

- Is the cuff size correct?
- Is there an undue 'white-coat' effect?
- Has the patient got very stiffened arteries that won't compress during sphygmomanometry producing 'pseudohypertension'?

Poor adherence to the prescription, poor response to desirable lifestyle change or concomitant use of counteracting drugs (especially non-steroidal anti-inflammatories) may also be relevant. The patient may indeed have an unsuspected cause of secondary hypertension or irreversible target organ damage which renders treatment less effective, and the influence of sleep apnoea might also usefully be explored.

Referral to a specialist

Most of the above strategies can be explored in general practice, others may be helped by referral to a specialist. Certainly, most moderate hypertension can be handled in primary care and full use can be made of single and combined prescription of drugs from the four classic 'ABCD' drug groups, with the possible substitution of an ACEI with an ARB where necessary. A patient with severe or resistant hypertension might require special investigation for a cause of secondary hypertension, particularly where this occurs at a younger age. Where there is a complex history of past use of different drugs with differing outcomes, it is important to provide this with a referral, tedious though this may be to detail. Patients have only a limited memory of which drugs they have tried and which produced any particular side effect. Provision of results of recent investigations is also helpful and may avoid wasteful duplication. If, for a period, there is some combined management of the patient it is also helpful when there is continuing good 'two-way' communication. Many such issues for the hypertensive patient could probably be resolved without an actual personal appointment but by an exchange of information alone. Hopefully medical culture is evolving to make this a realistic regular and efficient avenue in the future.

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Competing interests

In recent years I have given consultancy advice to AstraZeneca and have given invited talks at meetings sponsored by AstraZeneca, Merck Sharp and Dohme and by Pfizer. I am also a member of the Cardiovascular Subcommittee of PHARMAC's Pharmacology and Therapeutics Advisory Committee.

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