There is a positive correlation between blood pressure and subsequent risk of cardiovascular diseases, including heart attack and stroke. The slope of the relationship is affected by other risk factors such as total and high-density lipoprotein cholesterol levels, smoking status, diabetes and the presence or absence of left ventricular (LV) hypertrophy (Fig 1). There is good evidence that treatment of hypertension reduces cardiovascular risk, but the absolute degree of benefit to be gained depends upon the initial level of risk. For this reason, arbitrary definitions of blood pressure levels above which treatment should begin are no longer considered justified. This article considers the causes, diagnosis and treatment of hypertension.

Causes

Despite substantial advances in the understanding of basic vascular biology, most patients with high blood pressure are labelled as suffering from essential hypertension. Although (by definition) the causes of essential hypertension remain unknown, environmental factors may affect blood pressure and therefore contribute to the presentation of hypertension (Table 1). Furthermore, the list of causes with a known underlying mechanism (secondary hypertension) has expanded considerably (Table 2).
Table 1. Common and important environmental/acquired factors that increase blood pressure either acutely or chronically.

- Obesity
- High dietary sodium intake
- Drugs (non-steroidal anti-inflammatory drugs, glucocorticoids, combined oral contraceptive pill, cyclosporin, erythropoietin)
- Anxiety
- Alcohol intake (>3 units/day)

Diagnosis

Blood pressure should be measured in both supine and standing positions. Unless it is very high (see below) the diagnosis of hypertension requiring treatment should not be made on the basis of readings made on a single occasion. There is seldom a need to rush into treatment, and ideally several measurements of blood pressure should be made over some weeks. Clinical trials suggest that habituation to blood pressure recordings can cause substantial drops in pressure – often in the region of 10 mmHg systolic and 5 mmHg diastolic. Most guidelines make the following recommendations for assessment of hypertension:

- for mild hypertension, assessment over about 12 weeks is reasonable before deciding whether to start treatment
- for pressures of 160–179/100–109 mmHg, assessment can take place over 4–12 weeks (3–4 weeks if target organ damage is evident)

Table 2. Overview of causes of hypertension.

| Cause                        | Tests                                      | Specific treatments                      |
|------------------------------|--------------------------------------------|-----------------------------------------|
| Metabolic/Hormonal           |                                            |                                         |
| Hyperaldosteronism           | Renin & aldosterone levels. Adrenal CT/MRI| Spironolactone. Surgery                 |
| Cushing’s syndrome           | Cortisol & ACTH. CT/MRI                    | Specific treatment is for Cushing’s disease rather than for BP |
| Phaeochromocytoma            | Catecholamines/VMA. MIBG scan. CT/MRI      | Combined α and β blockade. Surgery      |
| Renal                        |                                            |                                         |
| Acute or chronic renal failure| Specific tests for individual causes of renal failure | Usual drugs for lowering BP |
| Renal artery stenosis        | Renal ultrasound. Angiography (definitive test). Elevated renin & aldosterone levels | Caution with renally excreted drugs |
|                               |                                            | Usual drug treatment of BP except that ACE inhibitors may worsen renal function. |
|                               |                                            | Angioplasty or surgery may provide definitive treatment |
| Structural                   |                                            |                                         |
| Coarctation of aorta         | CXR. Echocardiogram. Angiogram             | Surgery                                |
| Renal artery stenosis        | See above                                  | See above                               |
| Single gene defects          |                                            |                                         |
| Liddle’s syndrome*           | Na(+) , K(+), renin & aldosterone both suppressed. Genotype | Low salt diet. Amiloride or triamterene |
| Glucocorticoid-remediable aldosteronism** | Na(+) , K(+), renin suppressed & aldosterone elevated. Presence of 18-oxocortisol in urine. Glucocorticoid suppressible. Genotype | Dexamethasone |
| Syndrome of apparent mineralocorticoid excess† | Na(+) , K(+), renin & aldosterone both suppressed. Genotype | Dexamethasone |
| Other                        | None                                       | Discontinue if possible                 |
| Drugs (NSAIDs, etc)          |                                            |                                         |
| Pregnancy (pre-eclampsia)    |                                            |                                         |

ACE = angiotensin-converting enzyme; BP = blood pressure; CT = computed tomography; CXR = chest x-ray; MIBG = metaiodobenzylguanidine; NSAID = non-steroidal anti-inflammatory drug; VMA = vanillylmandelic acid

* Autosomal dominant disorder resulting from activating mutations in the β and γ subunits of the epithelial sodium channel which cause constitutive sodium absorption from the distal convoluted tubule of the kidney. Amiloride and triamterene are specific blockers of this channel.

** Autosomal dominant disorder caused by the inheritance of a chimaeric gene comprising the promoter of 11β-hydroxylase and the coding region of aldosterone synthase. Aldosterone synthesis is regulated by ACTH (rather than by angiotensin II), which explains both the high circulating levels of aldosterone and the steroid suppressibility of the hypertension.

† Autosomal recessive disorder caused by mutations in 11β-hydroxysteroid dehydrogenase type II – a renal enzyme which normally metabolises cortisol, thereby protecting the renal mineralocorticoid receptor from activation by glucocorticoids. Mutations in this enzyme allow endogenous glucocorticoids access to the renal mineralocorticoid receptor causing excess salt and water retention. The disorder is also amenable to treatment with low-dose exogenous steroid sufficient to suppress endogenous ACTH production.
Table 3. Essential investigations for all patients with hypertension.

| Test                                | Assessing risk/damage | Screening for causes |
|-------------------------------------|------------------------|----------------------|
| Total and HDL cholesterol           | Yes                    | Renal                |
| Creatinine                          | Yes                    | Renal                |
| Blood sugar                         | Yes                    | Renal                |
| ECG                                 | Yes                    | Renal                |
| Urinalysis (blood protein)          | Yes                    | Renal                |
| Serum K⁺ and Na⁺/K⁺ ratio           | No                     | Hormonal/metabolic   |

HDL = high density lipoprotein

- for pressures of 180–219/110–119 mmHg, treatment should be started within 1–2 weeks (see below for emergency treatment).

Other factors such as age, concomitant disease, speed of onset of hypertension (if known) and presence of additional risk factors should also be taken into account when considering how soon to treat. In any patient who is overly anxious, has a resting tachycardia, or in whom measurements are variable, the possibility of ‘white coat’ hypertension should be considered. In this situation, repeated measurement by a nurse or 24-hour ambulatory blood pressure recording may help to establish the true level of blood pressure.

Investigations

Investigations of patients with hypertension have two main purposes:
- to identify possible underlying causes
- to estimate the overall level of cardiovascular risk.

The essential investigations for all patients, together with the objectives of the tests, are shown in Table 3. Additional tests will be required for any patient with a suspected underlying cause for the hypertension (Table 2). Specific tests are indicated on the basis of the findings of initial screening investigations and/or specific clinical signs or symptoms (renal bruit, delayed/absent femoral pulses, etc). Secondary causes should be sought and excluded in:

- very young patients or children with hypertension
- young patients (<35 years) with moderate to severe hypertension
- individuals with very variable blood pressure (to exclude phaeochromocytoma)
- patients of any age with treatment-resistant, severe or malignant hypertension.

The finding of a low serum potassium or a high sodium/potassium ratio should prompt screening for underlying metabolic causes of hypertension, particularly Conn’s syndrome.

**Treatment of essential hypertension**

Treatment of essential hypertension should be considered as part of an overall package of cardiovascular risk reduction. Several tables are available to aid calculation of risk, but simple computer programs offer a more accurate estimate. In order to achieve adequate risk reduction, individuals should be encouraged to stop smoking and, when appropriate, lipid-lowering therapy and/or aspirin introduced. Figure 2 illustrates the impact of blood pressure lowering alone, compared with combined risk factor reduction in a 69 year old man. When a decision has been taken that blood pressure lowering is required, non-drug measures should be attempted first. Table 4 indicates the average blood pressure lowering effect achieved by lifestyle changes. Additional risk reduction may result from lifestyle changes through mechanisms independent of any effects on blood pressure.

If blood pressure remains a significant risk factor, despite appropriate lifestyle changes or intervention in other areas (eg stopping drugs that may increase blood pressure), antihypertensive drug treatment may be indicated. On average, each of the commonly used classes of antihypertensive drugs would be expected to lower blood pressure by about 5–8 mmHg. The risk reduction achieved is nearly complete for stroke: that is, patients rapidly reach a level of risk similar to individuals with blood pressure equivalent to the new treated level. Risk of myocardial
Table 4. Mean impact of lifestyle changes on blood pressure.

- Weight reduction: 1–2 mmHg for each 1 kg lost\(^{11}\)
- Sodium restriction from 10 g/day to 5 g/day: 5/3 mmHg\(^{12}\)
- Stress management: 0 mmHg\(^{2}\)
- Regular aerobic exercise (at least 3 times/week): 4/3 mmHg\(^{13,14}\)
- Increase intake of fruit and vegetables from 2 to 7 portions/day: 7/3 mmHg\(^{15}\)
- Avoid excess alcohol intake (change depends on amount consumed)

Note: It is not known to what extent these effects are additive, although evidence suggests that weight loss and sodium restriction produce greater weight loss than either alone

infarction, however, appears to reduce only to about 50–70% of that expected\(^{7}\). The reasons for this are not yet known, and the full extent of benefit is not clear.

Table 5 lists the recommended choices of drug, together with an indication of racial differences in response to drug treatment, and logical combinations of drugs known to produce additional effects when used together. When treating women of child-bearing age, every attempt should be made to use drugs known to be safe in the first trimester of pregnancy. Beta-blockers or thiazide diuretics are usually effective, and are considered safe\(^{8}\). Once pregnancy has been established it makes sense to switch to methyldopa since there is extensive experience of its use in pregnancy, and it appears safe. Methyldopa is not advised before pregnancy; it has numerous unwanted effects and increases prolactin levels, thereby potentially decreasing fertility.

Once a decision has been taken to treat an individual with essential hypertension, it makes sense to try to reduce both systolic and diastolic pressure to normal levels. Calculation of overall risk and expected risk reduction is useful to identify target blood pressure levels for individuals\(^{9}\). Reduction of blood pressure to normal is particularly important in patients with diabetes as it delays long-term vascular complications. The reduction in pressure is probably most important, rather than any specific effect of individual drugs. None the less, there is some evidence that angiotensin-converting enzyme (ACE) inhibitors may have advantages in preventing deterioration of renal function in diabetic patients with microalbuminuria\(^{9}\).

Treatment of secondary hypertension

The treatment of secondary hypertension is specific, depending on the underlying cause. An outline is provided in Table 2.

Emergency treatment

Oral drug therapy will suffice for virtually all cases of hypertension. In most instances, there is no need to reduce blood pressure to normal quickly, and a gradual fall over days or weeks is the desired option. However, in some situations it is necessary to start treatment immediately and lower blood pressure more rapidly:

- accelerated or malignant hypertension (grade III or IV retinopathy, with haemorrhages, cotton wool spots, papilloedema)
- very severe hypertension (>220/120 mmHg)
- hypertensive LV failure
- hypertensive encephalopathy
- dissecting aortic aneurysm
- pre-eclampsia.

Admission to hospital and bed rest usually result in a small fall in blood pressure, but immediate drug therapy is indicated and specific measures may be needed if an underlying cause is found. For severe and malignant hypertension, a fall in pressure over 3–4 days is acceptable. If LV failure, hypertensive encephalopathy or dissecting aortic aneurysm is present, the aim should usually be to lower blood pressure over 24–48 hours, reducing diastolic pressure to 105–110 mmHg. However, in some patients (particularly pregnant women) it may be necessary to reduce pressures to normal within this time period, but too rapid a fall in pressure can lead to retinal damage and blindness. Very occasionally, it is necessary to give intravenous therapy, and a nitric oxide (NO) donor (sodium nitroprusside or glyceryl trinitrate) or diazoxide may be used. NO donors may be particularly useful in the presence of hypertensive LV failure. Beta-blockers are usually given if dissection is suspected. Sublingual nifedipine should be avoided as its effects are erratic and dangerous falls in pressure can occur.

Table 5. Recommended drug options.

- First-line: thiazide diuretic or beta-blocker\(^*\)
- Second-line: ACE inhibitor* or long-acting calcium channel blocker
- Third line: angiotension II antagonist (for those intolerant of ACE inhibitor)*, alpha-blocker
- Additive combinations for dual therapy:
  - beta-blocker: add thiazide or long-acting dihydropyridine calcium channel-blocker
  - thiazide: add beta-blocker or ACE inhibitor

\(^*\) Effect enhanced by sodium restriction. Often not suitable for monotherapy in black patients (particularly if elderly)

\(^{ACE} = \text{angiotensin-converting enzyme}\)
simple remedy. Even in the most severe cases, it is seldom necessary to use more than three or four drugs to bring down the pressure. Indeed, the entire formulary for blood pressure treatment need include only six or seven individual drugs. Common reasons for treatment failure include:

- non-adherence to therapy (often exacerbated by poor provision of information)
- diet: a persistent high salt diet will render certain drugs (eg beta-blockers and ACE inhibitors) less effective
- concomitant drug therapy that blocks antihypertensive action (eg non-steroidal anti-inflammatory drugs)
- wrong drug(s): for example, use of a beta-blocker as monotherapy in a black patient, or adding a beta-blocker to an ACE inhibitor as dual therapy
- wrong dosing: a common problem is that short-acting drugs are given once a day, so blood pressure is often found to be elevated several hours after treatment.

True resistance to treatment requires further investigation for possible underlying causes (Table 2).

Future treatments

It is likely that more cases of secondary hypertension will be diagnosed as advances in genetics and vascular biology identify new causes with specific treatments. New antihypertensives in development include antagonists of the potent vasoconstrictor endothelin, novel donors of NO and modulators of the natriuretic peptides. Most cases of hypertension can, however, be adequately treated with existing drugs. New drugs would need to show substantial advantage in terms of reduction of mortality or morbidity to justify their use in any but the most resistant or specialised forms of hypertension.

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