STATE OF THE ART REVIEW

Does it matter how blood pressure is reduced?

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Introduction
Vascular pathology in hypertension can be roughly divided into three categories; bursting, strengthening and occluding (Table 1). Fibrinoid necrosis of arterioles and Charcot–Bouchard aneurysms upon penetrating arteries at the base of the brain appear to be caused by the elevation of pressure itself. The rate of rise of pressure, age and smoking may influence the severity of the lesions and the pressure level at which they develop but they are modulating not causative factors. Blood pressure reduction by many different means (salt restriction, ganglionic blockade, α-adrenoceptor blockade, vasodilatation etc.) will halt the progression of these lesions. For malignant hypertension the question posed by the title of this article can be answered with a firm ‘No!’.

Most patients under treatment today never suffered from malignant hypertension and the vascular disease that afflicts them is atheromatosus and occlusive rather than necrotic and bursting. The relationship between the level of blood pressure and the pathogenesis of this type of vascular disease is much less clearly established in a mechanistic sense, although the fact of the relationship cannot be disputed. Myocardial infarction is the main cause of death in these patients. Although high blood pressure is an important risk factor, others, such as lipids, smoking and diabetes, make a major independent contribution. It would be unreasonable to expect that the effect of blood pressure reduction would be so clear and direct upon this type of disease as it is with malignant hypertension and such as has proved to be the case [1–5]. In aggregate the trials [1, 2, 4, 5] show a reduction in mortality from myocardial infarction but it did not reach statistical significance in any one of them. As myocardial infarction alone exceeds the sum of all other hypertension-related deaths this result is depressing. In such circumstances, accessory pharmacological properties may be important, especially if they influence the likelihood of death from myocardial infarction. The general increase in mortality noted in the actively treated group in the clinical trials of the lipid-lowering agent clofibrate [6] is a warning that apparently beneficial pharmacological actions do not necessarily bring about the desired outcome. Thus, in benign hypertension, it may be worth exploring the proposition that the means of lowering the blood pressure does matter.

The efficacy of anti-hypertensive therapy has been demonstrated in the randomized controlled trials already cited, but the magnitude of the benefit declines steeply with less severe blood pressure elevations. The difference in mortality between the active and placebo treated groups was 43.7 per 1000 patient years in the first Veterans trial report (diastolic pressure 115–129 mmHg) [1] and 17.0 in the second (diastolic pressures 90–114 mmHg) [2]. These were hospital-based trials. In the Australian Trial [4], based on community screening, the difference in mortality was only 2.0 per 1000 patient years in those adhering to treatment (diastolic pressures 90–109 mmHg). As the benefits of treatment decline so questions about the quality of life during prolonged drug treatment become more important. Commonsense suggests that there

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<th>TABLE 1. Vascular pathology in hypertension</th>
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<td>Bursting</td>
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<td>(a) Fibrinoid necrosis</td>
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<td>(b) Charcot–Bouchard aneurysms</td>
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<td>(c) Dissecting aneurysm</td>
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<td>Strengthening</td>
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<td>(a) Muscle hypertrophy</td>
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<td>(a) Atheroma</td>
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<td>(b) Thrombosis</td>
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<td>(c) Embolization</td>
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must come a point at which the absolute benefits for the individual are so small that a relatively modest burden of symptoms and anxiety is not worthwhile. Less attention has been given to the quantification of side effects than to morbidity and mortality but this is now receiving more systematic study.

These two topics, blood pressure independent factors in the outcome of treatment and the burden of symptoms caused by different drugs, form the substance of this lecture. As the subject is a large one I shall confine myself to standard step care regimens consisting of diuretic, β-adrenoceptor blocker and vasodilator, and most of my attention will be focused upon the first two members of this triad.

Thiazide diuretics

The hypotensive action of chlorothiazide was noted shortly after its introduction as a natriuretic agent in patients with oedema. Diuretics have become one of the cornerstones of most regimens of hypotensive therapy because of their ease of use and freedom from disabling side effects. The dose–response curve is flat [7] and circulatory adaptations to standing and exercise are unimpaired. The metabolic effects of hyperuricaemia, hyperglycaemia and hypokalaemia were noted during early trials of chlorothiazide but have been regarded as minor problems apart from special situations such as the concomitant use of digitalis glycosides. New data may necessitate a re-appraisal of this reassuring opinion, at least in the context of indefinite treatment of very mild hypertension.

Diabetes

The literature contains conflicting opinions about the extent and even the existence of diabetes provoked by thiazide diuretics. Our first study of 137 patients who received one of four different diuretics for a year did not show any decrease in glucose tolerance in the group as a whole, although a follow-up after 5 years of treatment in 67 patients showed a significant deterioration [8, 9]. A study in a group of elderly patients carried out by the European Working Party on Hypertension in the Elderly demonstrated progressive deterioration of glucose tolerance during diuretic therapy [10]. The British MRC Hypertension Trial [11] has also shown a significant rise in blood sugar in patients treated with bendrofluazide in a dose of 10 mg daily. On the other hand, a recent study with a low dose of bendrofluazide did not show any significant deterioration in glucose tolerance over a 5 year period [12].

Recently we restudied 36 of our original 137 patients, most of whom have been on bendrofluazide 10 mg daily for 12–15 years. Fifty-eight per cent fulfilled the WHO definition for glucose intolerance or diabetes and there has been a highly significant rise of 28.4 mg/dl in the fasting blood sugar. Although there are no directly comparable control data it seems that these changes exceed those seen simply as a result of ageing. The disturbance of glucose tolerance in most patients is mild and easily managed. A very important question is how far these changes in glucose tolerance are atherogenic. There is good epidemiological evidence that glucose intolerance is a risk factor for myocardial infarction [13] and there is no reason to believe that diuretic-induced hyperglycaemia is any safer than spontaneous maturity-onset diabetes. The change in glucose tolerance on a year to year basis is small but its cumulative effect may be adverse.

There are several possible strategies for minimizing the problem. One is to limit the dose of diuretic used to the equivalent of 2-5 mg of bendrofluazide daily, possibly combined with moderate dietary salt restriction, another is to avoid the use of diuretics in the obese and the elderly. This is easier said than done because so many other hypotensive agents cause retention of salt and water.

Hypokalaemia

The importance of extracellular potassium concentration in myocardial contractility has been recognized since the time of Ringer [14]. Provocation or exacerbation of cardiac arrhythmias by hypokalaemia, especially in relation to digitalis glycosides, has been studied extensively [15–19]. In retrospect it is surprising that most of the attention directed towards potassium balance with diuretics was concentrated upon the total exchangeable pool and not the plasma concentration. Two factors have caused a re-appraisal of the position. The first has been evidence from clinical trials which have shown an increased incidence of ventricular premature beats in patients treated with thiazide diuretics [20]. Although it has not been proved that hypokalaemia is responsible this seems the most likely explanation. A moderate increase in the number of ventricular extrasystoles need not have an adverse effect but there is evidence that when these occur early during repolarization they may precipitate ventricular fibrillation [21]. The
second factor has been reports that patients who are admitted to hospital after an acute myocardial infarction have a worse prognosis for developing serious ventricular arrhythmias if they are hypokalaemic [22].

As myocardial infarction is the major cause of death among treated patients with mild hypertension, the possibility that mild hypokalaemia may increase risk deserves serious consideration.

Fisch [23] suggested that hypokalaemia increases ectopic activity by enhancing automaticity. It may also delay AV conduction and this combination may facilitate re-entrant arrhythmias, especially in a myocardium with uneven electrical propagation of the action potential due to patchy ischaemia. An important additional factor may be the action of catecholamines, especially adrenaline, at times of stress such as fear, exercise, angina or myocardial infarction. Adrenaline has three distinct arrhythmogenic actions. The first is a direct action upon the myocardial cells and conducting tissue [24], the second is to stimulate lipolysis and thereby increase the concentration of free fatty acids, and the third is to produce an acute reduction of serum potassium.

Isabelle Macquin and Morris Brown in our group have recently demonstrated that adrenaline infusions at concentrations found during severe stress can cause a sharp reduction in the serum potassium concentration by 0.5–0.6 mmol/l. The acute effect of adrenaline release upon a background of an already low extracellular potassium concentration induced by thiazides might cause temporary severe hypokalaemia. This factor, added to the ability of adrenaline to facilitate delayed after-depolarization [25, 26] may explain the increase in ectopic beats. Intravenous injection of adrenaline is one of the standard methods of provoking arrhythmia in animals [27] so the eventual effect would be to combine a predisposition to arrhythmia with a powerful arrhythmogenic agent.

These arguments suggest that hypokalaemia caused by thiazides can no longer be dismissed as trivial, even if the mean reduction of the plasma concentration is only about 0.6 mmol/l. There are two possible strategies for dealing with the problem. The first is to prevent hypokalaemia with potassium supplements or potassium-conserving diuretics. The second is to combine thiazide diuretics with a β-adrenoceptor-blocking drug to inhibit both the hypokalaemic and arrhythmogenic effect of adrenaline. A combination of the two would cover both eventualities although it would not deal with the problem of hyperglycaemia or hyperuricaemia unless the diuretic dose were kept low.

The available evidence suggests that, for equal reductions of blood pressure, thiazide diuretics may have an unfavourable effect upon the outcome of ischaemic heart disease, while β-adrenoceptor-blockers may have a beneficial one. The issue is such an important one that it is highly desirable that there should be direct evidence in hypertensive patients to back up the inferences and theoretical arguments upon which this conclusion is based. The British Medical Research Council Hypertension Trial [28] and a trial in progress in Sweden both involve comparisons of diuretic and β-receptor-blocking drugs and these may provide an answer. The question of combinations of diuretics and β-receptor-blocking drugs, whose popularity is rapidly increasing, will remain without a direct answer. Therapeutic practice often changes more quickly than trials can be mounted to validate or confound it.

β-Adrenoceptor blockade

The blood pressure-lowering action of β-adrenoceptor-blocking drugs was noted by Prichard & Gillam [29] during a clinical trial in angina pectoris. The use of the drugs in hypertension has increased rapidly and they are the second step in most antihypertensive regimens although, increasingly, they may be the first choice. β-Adrenoceptor blockade lowers the standing and lying pressures to a similar extent and greatly reduces the normal rise in blood pressure during exercise. The lack of postural effect is a considerable advantage, while the effect during exercise benefits angina because it reduces left ventricular work. The exercise effect is less clearly advantageous for hypertensive patients because restriction of the rise in cardiac output makes the patient feel fatigued. β-Receptor-blocking drugs have a highly specific competitive antagonism at the β-adrenoceptor. Non-specific pharmacological effects such as membrane actions are not seen at the concentrations required to produce a high degree of antagonism at the β-receptor. In consequence β-receptor-blocking drugs have fewer unpredictable effects, although the consequences of their prime action are widespread, including inhibition of cardiac, vascular and bronchial β-receptors, effects upon lipolysis, glycogen mobilization etc. Serious, or potentially serious, adverse reactions include worsening of asthma, the practolol syndrome and carcino genesis. By far the most important positive quality of β-adrenoceptor-blocking drugs, apart from their action upon blood pressure, is
their favourable effect upon some aspects of ischaemic heart disease.

**Serious adverse effects and toxicity**

The two most important pharmacologically mediated adverse effects are provocation of asthma and slowing of recovery from hypoglycaemia. An acute attack of asthma can cause death [30] but there is little or no data to suggest that the use of β-adrenoceptor-blocking drugs has greatly increased asthma mortality. If the contraindications are observed most cases provoked by β-receptor blockers should be mild but the use of these drugs is now so widespread that contraindications are often overlooked. Concomitant use of β-receptor-blocking drugs and insulin, especially in patients with angina, has led to cases of prolonged hypoglycaemia but few fatalities have been reported [31].

The main concern about adverse effects of β-adrenoceptor blockade has been focused upon animal carcinogenicity tests and the oculo-mucocutaneous syndrome with practolol. Two β-adrenoceptor-blocking drugs pronethalol and tolazolol have been withdrawn from clinical trials because of animal carcinogenicity test findings. In neither case were the findings sufficient to conclude that the compound was itself a carcinogen. Neuroendocrine changes brought about by the drug may have been an important factor with tolazolol and the pronethalol findings were not reproduced in a subsequent study. Although there is no reason for specific concern about the drugs on the market these results do serve as a warning that prolonged and intense β-adrenoceptor blockade might have effects upon the type of tumours that occur spontaneously in man and possibly on their spread. No biological significance has yet been assigned to prolonged inhibition of the lymphocyte β-receptor in relation to immune surveillance but it is another aspect to keep in mind.

The skin, eye and peritoneal changes that afflicted about 1000 patients who took the selective β-adrenoceptor blocker, practolol, must count as one of the major drug disasters of recent history [32]. The mechanism of toxicity appears to have been immunologically mediated and antibody directed against intercellular ground substance was demonstrated by immunofluorescence in skin biopsies [33]. An antibody against a practolol metabolite has also been found in the plasma of patients with the syndrome but not in other patients who took the drug.

Despite the existence of scattered case reports of eye, skin and peritoneal changes with other β-adrenoceptor blockers the complete syndrome appears to have been unique to practolol. Thus the syndrome does not appear to have any direct relationship to β-adrenoceptor blockade. This does not mean that the syndrome might not occur with another β-adrenoceptor blocker, for they all have considerable structural similarities, but competitive inhibition of the β-receptor, *per se*, should not give rise to concern, in this respect.

**Myocardial infarction**

Inhibition of the myocardial β-receptor reduces left ventricular work and oxygen demand, especially during intense sympatho-adrenal stimulation such as occurs on exercise or during fear and anger. This action is the basis for the use of these drugs in the prophylaxis of angina pectoris. The same type of action could be employed to limit the degree of ischaemic necrosis in the outer layers of myocardium in an area supplied by an acutely occluded artery. This expectation has been supported by clinical studies which have investigated the use of atenolol and propranolol to limit the size of an infarct when treatment is started within 4 h of the onset of pain. This treatment can reduce the area under the time–concentration curve of creatine phosphokinase to about 68% of the non-treated value [34, 35]. It is not yet clear whether limitation of the volume of necrosis will have a beneficial effect upon mortality or later morbidity from arrhythmia or heart failure.

The most important property of β-adrenoceptor blockade in cardiac ischaemia has been the demonstration of a reduction in mortality amongst victims of a myocardial infarction during the subsequent 3 years if treatment with a β-adrenoceptor-blocking drug is started within 1 month of the infarct. Amongst the compounds that have shown such an action are practolol, alprenolol and, particularly, timolol [36–38]. A trial with propranolol was discontinued on the grounds that it was unlikely to give a positive result because of the trend when about 1000 patients had been recruited [39]. The most convincing study was the Norwegian trial [38] with timolol, in which total mortality was reduced by 38% compared with the placebo-treated control group.

These findings cannot be translated without question to the prognosis of hypertensive patients who suffer a myocardial infarction but it has been suggested that the infarct rate is lower in hypertensive patients whose treatment includes a β-adrenoceptor blocker [40]. There is also the question of mechanism. Most commentators
assume that the action is primarily anti-arrhythmic but this ignores the evidence that drugs that are more effective in suppressing ventricular ectopics (procainamide, mexiletine) have not been shown to have a favourable effect upon survival. Presumably $\beta$-receptor-mediated arrhythmias must be crucial and the role of circulating adrenaline once against deserves notice. $\beta$- Adrenoceptor-blocking drugs would not only inhibit the direct effects of $\beta$-adrenoceptor stimulation in the heart but also the effects upon potassium.

Quality of life

When antihypertensive drugs were first used to treat patients with left ventricular failure or papilloedema their side effects were, rightly, regarded as mainly of nuisance value. The reduction in side effects when guanethidine and methyldopa replaced ganglionic blockade was one of the most important factors in the gradual extension of treatment to less severely hypertensive patients. The current popularity of thiazide diuretics and $\beta$-adrenoceptor-blocking drugs alone and in combination reflects a continuation of the same trend. While the reduction in really unpleasant side effects has been generally welcomed the corresponding lessening of the benefits of treatment as milder and milder patients are treated has received less attention. The question is where do the lines cross? At what point is the benefit of treatment negated, for an appreciable fraction of patients, by discomforts caused by the drugs even though these have no adverse effect upon morbidity of mortality from vascular disease?

One of the advances in clinical pharmacology has been recognition that it is as important to measure symptomatic side effects as it is to measure the main pharmacological action of the drug.

The method applied by C. J. Bulpitt and myself has been to ask patients to complete questionnaires concerning their symptoms. Another useful technique which has proved itself in the MRC Hypertension Trial [11] and the recent Norwegian timolol trial [38] is to collect very accurate information about why those patients who stop treatment do so [41–43].

The burden of side effects is greatly influenced by the psychological make up of the individual as well as age, sex and race. This is a problem in hospital clinics, which have a disproportionate number of patients who have been referred because their complaints of side effects made them a nuisance to their family doctors.

The MRC Hypertension Trial [11] has been of particular value in establishing incidence figures and significance because it incorporates placebo-treated groups. In other studies it has been necessary to compare patients taking one drug with those on another and it may be difficult to evaluate a side effect such as nausea if many different drugs can cause it. The subject is too large for a general exploration in a short lecture but can be illustrated by some examples.

Depression

Because we knew that some drugs used to treat hypertension can make patients feel depressed we incorporated a simple question asking if the patient was depressed and, if he was, whether it was severe enough for him or her to consult a doctor about it. The main reason for doing so was to evaluate reports that methyldopa causes depression. We found no evidence that methyldopa did cause depression but found an excess of 19% of patients receiving reserpine had this complaint. Depression induced by reserpine is well known but at the time this survey was done the largest dose used was 0.3 mg daily. An excess of one patient in five becoming depressed on this low dose is not trivial and yet there was a general impression that the problem of reserpine depression had been largely solved by reducing the dose.

Impotence

One of the few symptoms whose presence showed a positive correlation with poor compliance in our studies was impotence. The adverse effect of adrenergic neurone-blocking drugs upon ejaculation and $\alpha$-adrenoceptor blockade on erection is well known. The MRC Trial [11] has disclosed a significant increase in both complaints of difficulty in maintaining an erection and withdrawals from the drug for this reason in the bendrofluazide-treated group. The figure was even higher in patients taking hydralazine who were attending the Hammersmith Hospital Hypertension Clinic. The withdrawal rate for impotence in patients treated with bendrofluazide was 19.6 per 1000 patient years in the bendrofluazide-treated men in the MRC Trial. The comparable figure for propranolol was 5.5 and for placebo only 0.9. Questionnaires showed higher figures, with an excess of 12.5% of men after 2 years of treatment complaining of difficulty in sustaining an erection [11].
Gastrointestinal symptoms

Complaints of nausea, dizziness and headache are relatively common in patients taking a wide variety of drugs. In the MRC Trial there was a significant excess of these symptoms in patients on both of the active drug regimens with withdrawal rates of 16.3 per 1000 on bendrofluazide, 13.9 per 1000 on propranolol and 2.1 per 1000 on placebo in women. The rates in men were about half the rates in women.

Overall effect of minor symptoms induced by drugs

Several attempts have been made to assess the effects of antihypertensive therapy upon the quality of life in a general sense. One measure is the number of patients who stop taking a particular drug when treatment is still required. In the MRC Trial the cumulative percentage of withdrawals on bendrofluazide was 17.1% in men and 12.8% in women. The figures for propranolol were 15.5% in men and 18.8% in women. Withdrawals on placebo were about 5% in each of the groups.

Another method is to assess time lost from work. D. L. Sackett and his coworkers found that time lost from work due to non-specific illnesses was increased once patients knew they had hypertension [44]. Bulpitt et al. [42] assessed the total burden of symptoms before treatment and after a year of continuous antihypertensive therapy. The total number of symptoms changed little but symptoms lost such as morning headache were balanced by symptoms gained such as sedation and dry mouth. Mann [45] used a questionnaire designed to screen for mental illness in hypertensive patients before and during treatment. He found a decline rather than an increase in positive replies.

The prospect of millions of symptomless patients popping pills that slightly prolong their lives at the price of making them a little less happy every day that they survive is somewhat disquieting. Ultimately it is a decision in which informed patients will wish to participate and the replies will vary. Physicians should not be too displeased with patients who try out the available forms of therapy and decide that a slightly reduced life expectancy is an acceptable trade-off for greater comfort and enjoyment. But to make sensible decisions and to give good advice patients and doctors will need much more quantitative information about the soft pharmacology of side effects as well as the hard end-points of death and major disability.

If one patient in five started on diuretics and β-receptor blockers, the drugs with the least side effects, stops treatment within the disciplined framework of a clinical trial it is scarcely surprising that compliance figures in ordinary clinical practice appear to be low. Much more needs to be done in matching patients with predictable side effects and trying to devise regimens (e.g. moderate salt restriction, low-dose diuretic plus β-receptor blocker) that are acceptable to a higher proportion of patients.

Conclusion

The answer to the question posed by the title of this article in mild to moderate hypertension appears to be 'yes', both in respect of outcome and acceptability of treatment. The data available are not conclusive but they raise a question about the desirability of using thiazide diuretics as sole therapy, unless the dose is kept low, e.g. 2.5 mg of bendrofluazide daily. β-Adrenoceptor-blocking drugs appear to have the balance of advantage over thiazide diuretics as the first choice when treatment is initiated. One very important question is whether combinations of low doses of diuretics with potassium, potassium-conserving diuretics or β-receptor-blocking drugs will overcome some of the problems associated with the metabolic disturbances caused by thiazides. As about half the patients starting treatment for hypertension require more than one drug the question of combined treatment is particularly important. There is no real substitute for diuretics in step-care regimens because so many other drugs (guanethidine, methyldopa, hydralazine etc.) tend to cause fluid retention when used without one. While clinical trials of the classical type are appropriate to assess effects such as those upon potassium, cardiac arrhythmia and myocardial infarction, new types of study will be needed to assess the acceptability of treatment to random samples of the population. Strategies to improve the acceptability of treatment by simplifying regimens and reducing unwanted symptoms will be as important as physiological and biochemical indices of drug action. It is a different world from the one initiated by Horace Smirk when he began to treat malignant hypertension with injections of penicillin over 30 years ago.

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