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The hemodynamic effects of adrenergic blocking agents

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■ The various antihypertensive agents reduce blood pressure by different mechanisms. Alpha-1 receptor blockers reduce vascular resistance and maintain cardiac output. Chronic treatment with beta blockers without intrinsic sympathomimetic activity produces a fall in blood pressure which is associated with a fall in cardiac index and heart rate. Beta blockers with strong intrinsic sympathomimetic activity showed reduced heart rate during exercise. Labetalol reduces cardiac output and peripheral vascular resistance with little or no reduction in peripheral blood flow. Alpha-1 blockers are suitable for patients with active life-styles, with peripheral vascular disorders, or with high blood-cholesterol levels. Beta blockers are useful in patients who have tachycardia, palpitation problems, or angina pectoris, or who have survived a heart attack. They should not be used in patients with bronchial asthma, reduced peripheral blood flow, or heart failure. Labetalol reduces blood pressure in a somewhat larger fraction of patients than the pure alpha- or beta-blocking agents. It is hoped that its long-term results will include regression of cardiovascular damage, improved quality of life, and increased life expectancy.

□ INDEX TERMS: HEMODYNAMICS; HYPERTENSION; ADRENERGIC ALPHA RECEPTOR BLOCKERS; ADRENERGIC BETA RECEPTOR BLOCKERS

□ CLEVE CLIN J MED 1992; 59:193-200

THE MAJOR hemodynamic factors controlling blood pressure are cardiac output and total peripheral resistance. Hemodynamic alterations in hypertension differ in the early and later stages of the disorder.^{1,2} In a 20-year follow-up study of 76 hypertensive patients, we demonstrated hemodynamic changes over time from a pattern of high cardiac output and low resistance in young patients, to a pattern of low cardiac output and high resistance in older patients (*Figure 1*).³

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This article was produced by Consultants in Medical Education, Inc., Manhasset, New York, under an educational grant from Schering-Plough International.

In the early stages of hypertension, the sympathetic nervous system is overactive.⁴ Young subjects with mild hypertension have a characteristic hemodynamic pattern during rest of high cardiac output, rapid heart rate, normal stroke volume, and total peripheral resistance not different from normotensive controls. During exercise, however, the increase of the stroke volume is limited, and although the heart rate tends to be fast, cardiac output during submaximal exercise is slightly reduced. Total peripheral resistance during exercise does not fall to the same low levels found in normotensive controls.

As the hypertensive patient grows older, structural changes in the heart and in the arterioles are probably responsible for maintaining increased blood pressure. In most patients over age 40 with established hyper-

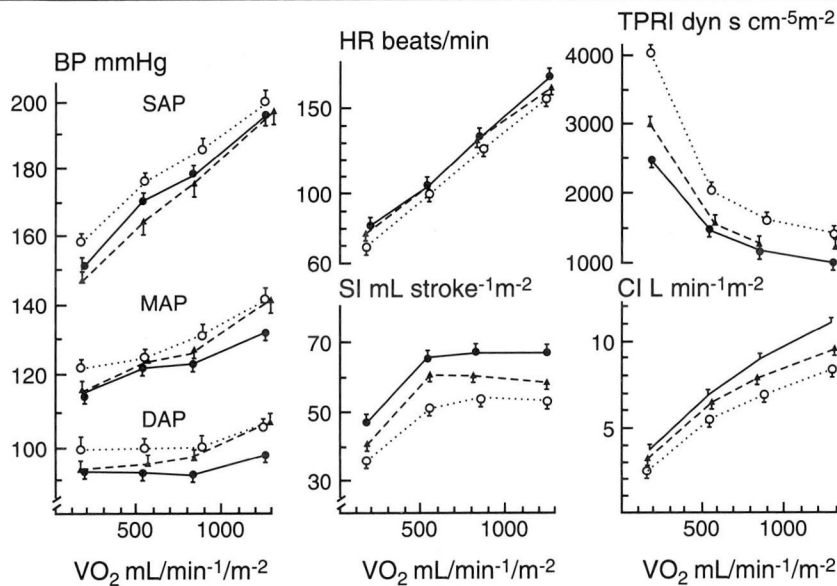


FIGURE 1. Hemodynamic alterations in essential hypertension over 20 years.³ Age at initial study 17-29 yrs. Mean values and SEM. VO_2 , oxygen consumption; HR, heart rate; CI, cardiac index; SI, stroke index; SAP, systolic arterial pressure; MAP, mean arterial pressure; DAP, diastolic arterial pressure; TPRI, total peripheral resistance index.

tension, the characteristic hemodynamic pattern during rest is normal cardiac output and increased total peripheral resistance. During exercise, cardiac output is subnormal and total peripheral resistance is markedly elevated.

In the later stages of severe essential hypertension, total peripheral resistance is greatly increased at rest and during exercise, often to more than twice the upper normal value. Heart pump function is markedly reduced with a fall in stroke volume when exercise load increases.

During the last decades of life, abnormalities in the heart are seen, including reduced compliance, reduced filling rate, increased left ventricular thickness, and left ventricular mass.⁵ Disturbances in the diastolic function probably are the first to occur. Recent echo-Doppler studies also have demonstrated reduced pump function during exercise.⁶ The increased vascular resistance is found in most vascular beds, although to varying degrees.⁷

The various antihypertensive agents reduce blood pressure by very different mechanisms. Drugs which act via the adrenergic receptors may induce widely different hemodynamic changes at rest and during exercise.⁸⁻¹¹ The following discussion briefly reviews the short- and long-term hemodynamic effects of these

commonly used antihypertensive drugs.

EFFECTS OF ALPHA BLOCKERS

Alpha receptors in the peripheral blood vessels mediate sympathetic nerve stimulation and are important for the regulation of the local blood flow and for the control of total peripheral resistance and, thereby, the blood pressure. For several decades, attempts have been made to reduce the effect of increased sympathetic tone on the resistance vessel by using alpha blockade. The first alpha blockers were nonspecific and blocked both alpha-1 and alpha-2 receptors at the nerve terminal and at the effector cells. Such

drugs (eg, phenoxybenzamine, dibenzylamine) induced vasodilatation, but when blood pressure fell, heart rate and cardiac output increased markedly. Consequently, the fall in blood pressure was modest, and these drugs could not be used for long-term treatment.¹²

The situation changed completely when selective alpha-1 receptor blockers were developed. These left the alpha-2 receptors undisturbed, thus preserving the negative feedback system for noradrenalin at the nerve terminal. This produced vasodilatation without reflex tachycardia.¹²⁻¹⁴

Acute and long-term effects

When an alpha-1 receptor blocker like doxazosin is injected as a single dose, total peripheral resistance falls rapidly, with no significant changes in heart rate or cardiac output. This results in an immediate fall in blood pressure, which is seen at rest and during exercise.¹⁰ In some patients, the fall in blood pressure is excessive, and in ambulatory patients this can induce the so-called "first-dose syncope reaction." In our series on doxazosin, 3 of 15 patients had a marked reduction in vascular resistance and blood pressure in the supine position after 1 mg of doxazosin was given intravenously, while heart rate did not increase. When the dose was reduced, these hypotensive reactions were not seen.¹⁰

Our 1974 study¹⁴ demonstrated that prazosin induced normalization of central hemodynamics at rest and during exercise (Figure 2). Significant reduction in total peripheral resistance was seen in all patients. Blood pressure was reduced about 10% in patients with mild to moderately severe essential hypertension. Heart rate did not change significantly, while exercise stroke index increased. As a consequence, the post-treatment cardiac index was higher than before treatment, inducing better total blood flow and normalization of arteriovenous oxygen difference. Our more recent studies on doxazosin and trimazosin have found the same effects.^{10,13} Our data have been supported by studies from several other laboratories.¹²

EFFECTS OF BETA BLOCKERS

The hemodynamic changes induced by beta blockers are different in the acute stage compared with long-term use, and are different for beta blockers with vs without intrinsic sympathomimetic activity (ISA).^{9,15,16}

Acute effect

The classic study of Tarazi and Dustan in 1972¹⁷ showed that, when propranolol was injected in a single dose, the initial response was a marked reduction in heart rate and cardiac output, a reflex increase in total peripheral resistance, and little immediate effect on the blood pressure. But after 8 months, peripheral resistance had fallen while cardiac output remained reduced and blood pressure fell.

The immediate response to beta blockade during supine rest is illustrated in more detail in Figure 3. During the first 2 hours after intake of epanolol, cardiac index was depressed approximately 20%, partly due to the drug's negative inotropic effect, and partly due to its chronotropic effect. However, the reduction in blood pressure was only 5%, since the fall in cardiac

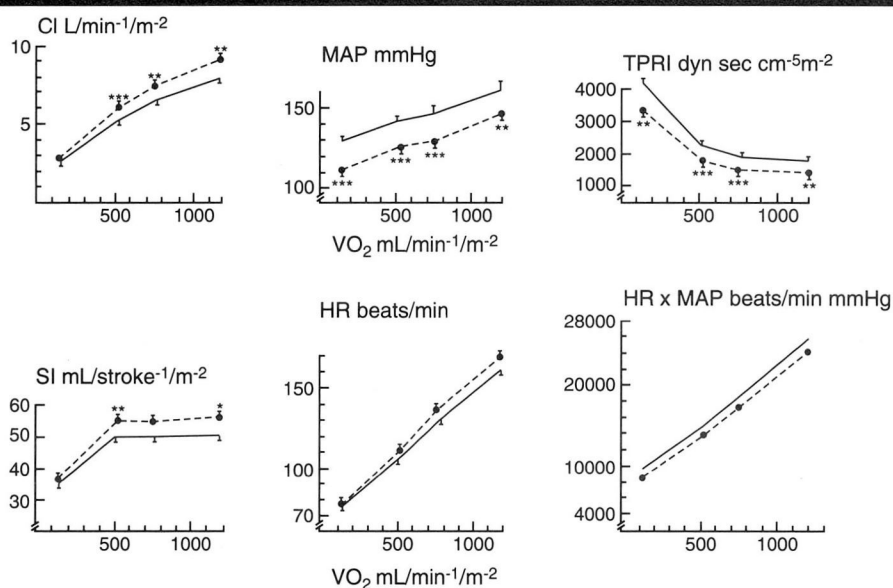


FIGURE 2. Central hemodynamics at rest and during exercise before (solid line) and during (broken line) 1 year treatment with prazosin (N=10).¹⁴ Mean values and SEM. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. VO₂, oxygen consumption; HR, heart rate; CI, cardiac index; SI, stroke index; MAP, mean arterial pressure; TPRI, total peripheral resistance index.

output was counteracted by a 20% increase in total peripheral resistance index. During the following 5 hours, total peripheral resistance fell towards pretreatment levels (for reasons still not quite understood), and the negative inotropic effect disappeared. The negative chronotropic effect was still present after 4 hours, when the fall in blood pressure was equivalent to the reduction in cardiac index.¹⁸

With other beta blockers (eg, timolol, atenolol), the blood pressure fall after 4 to 5 hours is usually greater than that achieved with epanolol.¹⁵

Chronic effect

The typical response to chronic (1-year) treatment with beta blockers without ISA is a fall in blood pressure at rest of about 15% to 20%, associated with a fall in cardiac index and heart rate of approximately 25%.^{9,15} With cardioselective drugs such as atenolol and metoprolol, there is a compensatory increase in stroke index during exercise, and the reduction in cardiac index is somewhat less than the fall in heart rate; nevertheless, it is between 20% to 25%. Total peripheral resistance usually does not fall below the pretreatment level. The response to long-term treatment with a nonselective beta blocker like timolol is a fall in cardiac index (25% to 30%) as shown in Figure

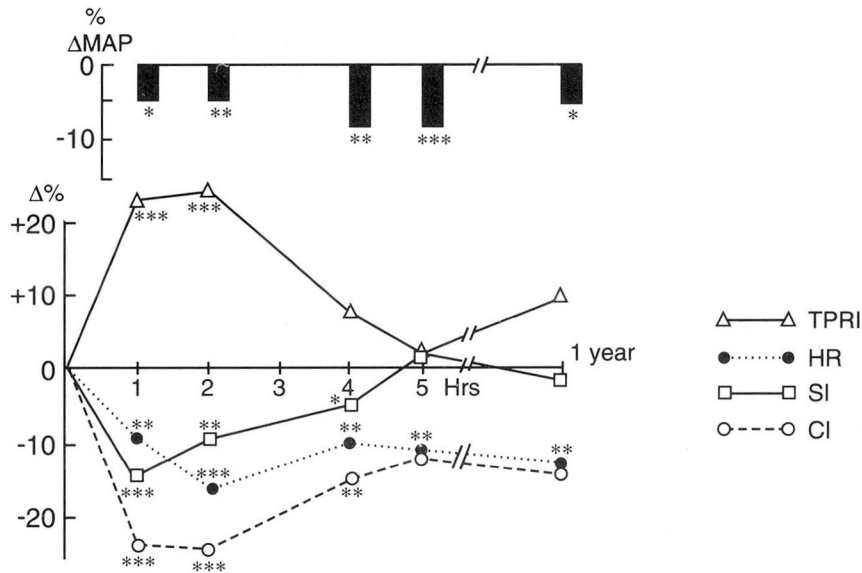


FIGURE 3. Immediate and chronic (1 year) hemodynamic changes (supine) induced by epanolol.¹⁸ Mean values and SEM. Significance values (asterisks) and abbreviations as in Figure 2.

4, while total peripheral resistance tends to increase. Since the beta-2 receptors are blocked, the high noradrenaline concentration present during exercise will induce alpha-1-mediated vasoconstriction without beta-2 vasodilatation.^{15,16,18}

ISA and beta blockade

Beta blockers with strong ISA exert different effects from those produced by beta blockers without ISA, particularly when sympathetic tone is low. Our study on pindolol⁹ showed no significant reduction in heart rate at rest, but during maximal exercise, heart rate was reduced 30 to 35 beats per minute. This reduction was less than that seen for beta blockers without ISA. Stroke index increased, and the reduction in cardiac index was less than that seen with other beta blockers with no ISA or only slight ISA. Total peripheral resistance fell slightly below pretreatment levels, possibly due to beta-2 stimulation, but the reduction was not statistically significant.

COMBINING ALPHA-1 AND BETA BLOCKADE

When alpha-1 and beta blockade are properly balanced, a marked reduction in blood pressure may be achieved as a result of reduction in total peripheral resistance and reduction of cardiac output. Thus, when

the two different principles of blood pressure reduction are used together, a fall in blood pressure of 25% or even more may be obtained with relatively little reduction in blood flow, especially during exercise.¹⁹ These effects may be achieved with single agents, such as labetalol.

Labetalol acts as a non-selective beta blocker and an alpha-1 blocker.^{19,21} When a 50-mg bolus dose is injected, a rapid fall in blood pressure (17% to 22%) is induced, and a consistent decrease in peripheral resistance is achieved (13%, on average). In general, only a slight reduction in cardiac index is seen.²² Similar

responses have been reported by others.²³⁻²⁶

We studied the hemodynamic changes induced by chronic labetalol therapy after 1 year and after 6 years in 15 men with mild to moderately severe essential hypertension.¹¹ Blood pressure was reduced markedly (22%) at rest and during exercise. After 6 years, total peripheral resistance was reduced considerably, cardiac index had returned to the pretreatment level, and stroke index had increased. The major results of this study are shown in Figure 5. Similar long-term results have been described by others, and it is generally agreed that during chronic treatment the reduction in cardiac index is small, since the stroke index increases and compensates for the fall in heart rate.²⁵ The patients in our study have remained on labetalol for more than 10 years with good blood pressure control, and all continued working until retirement at 67 to 70 years of age.

THE CONSEQUENCES OF HEMODYNAMIC CHANGES

The most important therapeutic principle in patients with hypertension and reduced renal function is to reduce blood pressure.²⁷ However, the different hemodynamic effects of various antihypertensive agents affect regional blood flow differently, and effects on target organs such as the heart and the blood vessels may vary.

Alpha blockers

Alpha-1-receptor blockers reduce vascular resistance and maintain cardiac output. However, since they do not reduce heart rate, the effect on the heart rate-blood pressure product is quite modest; therefore, they seem unsuitable for treatment of hypertensive patients with angina pectoris.

Prazosin reduces both preload and afterload, thus it might be seen useful in patients with hypertension and congestive heart failure. However, though initial studies indicated that prazosin was useful for the acute treatment of heart failure, recent studies indicate that tachyphylaxis develops, for reasons not quite understood.¹² In most studies prazosin has been associated with only small changes in renal blood flow.²⁸ Early studies have indicated a slight increase in cerebral blood flow.¹²

In recent years, alpha-receptor blockers have attracted great interest because they have been found to induce favorable changes in blood lipid levels. Earlier studies²⁹ showed that prazosin induced an increase in high-density lipoprotein, and this has been supported in recent studies.³⁰ However, it is disputed whether the effects of alpha-receptor blockers on blood lipids are of any significance in the prevention of arteriosclerosis, since beta blockers that increase blood cholesterol have been shown to reduce atherosclerosis in cholesterol-fed rabbits.¹⁵ It is possible that the rheologic and hemodynamic effects of alpha blockade (changes in stress on the artery, and flow turbulence) are more important than its effect on blood lipid levels in preventing arteriosclerosis.

Beta blockers

The most obvious effect of beta blockers without ISA in hypertensive patients is a marked reduction in the heart rate-blood pressure product, and in the work load on the heart. Many studies have shown that beta blockers induce regression of left ventricular hyper-

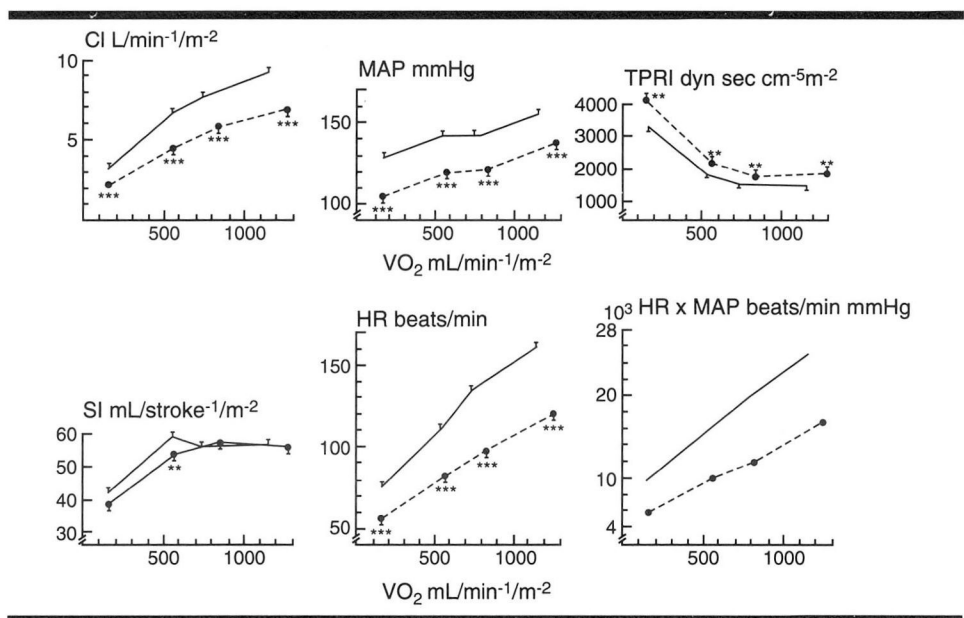


FIGURE 4. Central hemodynamics at rest and during exercise before (solid line) and during (broken line) 1 year treatment with timolol (N=16).⁹ Mean values and SEM. Significance values (asterisks) and abbreviations as in Figure 2.

trophy.³¹ Myocardial oxygen consumption is also reduced,¹⁵ but since cardiac output is reduced by approximately 20% during long-term use, while oxygen consumption during exercise is unchanged, there is an increase in the arteriovenous oxygen difference. The metabolic needs are covered by an increased extraction of oxygen from the blood.

The effects of beta blockers on various vascular beds are somewhat controversial. Forearm blood flow is reduced by nonselective beta blockade. Beta-1-selective drugs are expected to result in less reduction in peripheral flow. Drugs that induce the least increase in peripheral resistance are beta blockers with ISA, such as pindolol and oxprenolol.

The different types of beta blockers might have different effects on renal circulation. With most beta blockers like propranolol, the fall in cardiac output is associated with a fall in renal plasma flow, both after intravenous and prolonged oral administration. However, this is thought to be too small to be of clinical significance. Nadolol, on the other hand, increases renal blood flow in spite of reduction in cardiac output.¹⁵

During beta blockade, there is an increase in coronary vascular resistance in association with a fall in myocardial oxygen consumption, and myocardial

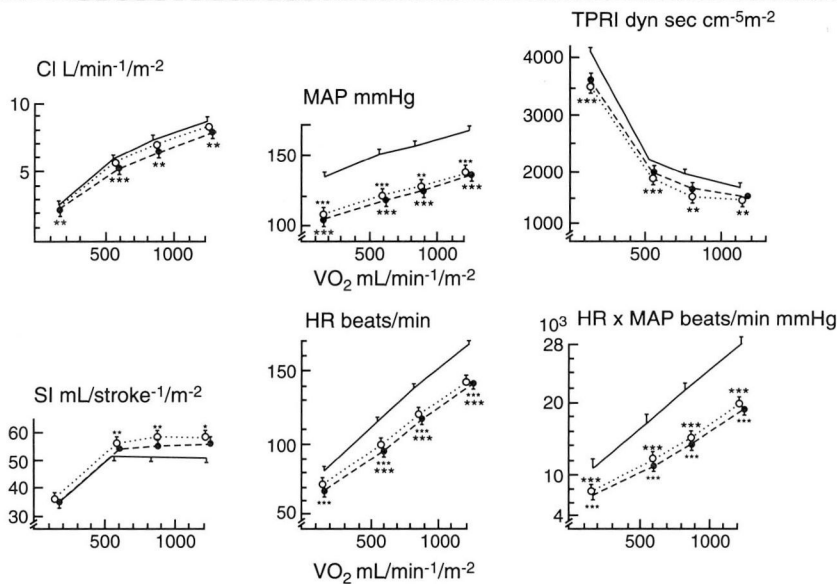


FIGURE 5. Central hemodynamics at rest and during exercise before therapy (solid line), after 1 year (dotted line), and after 6 years (broken line) of labetalol therapy (N=15).¹¹ Mean values and SEM. Small asterisks, statistical significance between first and second study; Large asterisks, statistical significance between first and third study. Significance values and abbreviations as in Figure 2.

oxygen balance is improved. Beta-1 selectivity does not seem to be important with regard to the coronary circulation.

Cerebral blood flow has not been affected in some studies but has been found to be decreased in others.¹⁵

Beta blockers reduce cardiac output markedly during exercise. Since the oxygen consumption is unchanged, there is an increase in arteriovenous oxygen difference.⁹ During the first weeks of therapy, many physically active patients complain of heavy legs. But beta blockers also reduce physical performance during chronic use, particularly during endurance activities. It has been observed that propranolol inhibits jogging performance up to 20% to 30%.¹⁵ The reduction in physical performance is due to hemodynamic changes and metabolic changes (reduction in lipolysis and reduction in free fatty acids available for muscle metabolism).

Labetalol

Most studies of the effect of labetalol on regional circulation have demonstrated a fall in vascular resistance of approximately the same magnitude as the reduction in total peripheral resistance. When labetalol is given intravenously, no significant changes in

forearm blood flow have been demonstrated. In patients with uncomplicated essential hypertension, effective renal plasma flow was found to have increased by 14% after labetalol treatment, though it decreased 19% after propranolol.²⁰ Intravenous administration of labetalol reduces coronary sinus flow and myocardial oxygen consumption, while coronary resistance does not change. Other studies have indicated that high doses of labetalol may decrease coronary resistance and increase coronary sinus flow. In general, it is assumed that labetalol induces less reduction in coronary blood flow than do ordinary beta blockers. Cerebral blood flow is not changed.

With respect to pulmonary circulation, no reduction in vascular resistance has been reported, and labetalol seems to have different effects on systemic and pulmonary resistance.²⁵

In our 6-year follow-up study of labetalol, central hemodynamics (pressure, total peripheral resistance, and stroke volume) were normalized during long-term treatment compared with 1-year results. The dose was practically unchanged, and the methods and hemodynamic setting were exactly the same for both studies, so the pharmacologic effects of the drug were expected to be similar. The different results could be due at least partly to differences in the arteriolar and left ventricular structure of the two studies. The functional changes seen during long-term treatment were beneficial. The result was a normal hemodynamic pattern in the treated hypertensive group compared to the detrimental hemodynamic pattern which we observed in patients with mild to moderate hypertension who were untreated over 10 to 20 years.³

WHICH DRUG FOR WHICH PATIENT?

In general, it is accepted that if nonpharmacologic measures such as weight reduction, smoking cessation,

physical exercise, and salt reduction do not lead to normotension, drug treatment should be started, especially when diastolic blood pressure is consistently above 100 mm Hg. My opinion is that, as long as no contraindications to any special class of drugs are present, then diuretics, beta blockers, calcium antagonists, angiotensin-converting enzyme inhibitors, and alpha blockers all have merit as first-line drugs. However, in patients with concomitant diseases, proper selection of an antihypertensive agent is necessary and may be based in part on the hemodynamic profile of the drug.

Candidates for alpha blockade

Alpha-1 blockers are suitable in patients with a very active life-style, particularly those engaged in sports and long-term endurance activities (eg, cross-country skiing, mountain hiking). They are also useful in patients with peripheral vascular disorders. Alpha blockers do not induce unwanted biochemical disturbances and have no detrimental effects on bronchi. Therefore, they may be used in patients with diabetes and obstructive pulmonary disease. They may be particularly useful in patients with high blood-cholesterol levels. Due to the possibility of postural hypotensive reactions with these agents, especially after the initial dose, it is important that the starting dose be low, and that the patient have the opportunity to lie down if an excessive postural hypotensive response should occur.

Candidates for beta blockade

Beta blockers are particularly useful in patients with hypertension associated with tachycardia and palpitation problems. In these patients, one can almost be certain that satisfactory blood pressure reductions will be obtained. Beta blockers are effective as monotherapy in approximately 60% of patients with mild to moderate hypertension. Since beta blockers have been shown to reduce reinfarction and mortality rates in patients who have survived a heart attack, they appear to be the logical choice in hypertensive patients who have suffered a myocardial infarction. To date, three different beta blockers have been found effective in controlled studies: propranolol, timolol, and metoprolol. Since beta blockers may reduce the heart rate-blood pressure product by 40% or more, they are particularly useful in patients with both hypertension and angina pectoris. In these patients beta blockers are obviously superior to alpha blockers. Beta blockers should not be used (or should be used cautiously) in patients with contraindications such as bronchial

asthma, reduced peripheral blood flow, or heart failure. Generally, they are not considered choice agents for individuals engaged in intensive sport activities.

Labetalol

Labetalol is a nonselective beta and alpha-1 blocker which effectively reduces blood pressure in a somewhat larger fraction of patients than the pure alpha or beta blockers. It reduces cardiac output and peripheral vascular resistance with little or no reduction in peripheral blood flow compared with beta blockers alone.

Since labetalol significantly affects the heart rate-blood pressure product, with marked reduction in blood pressure and reduction in heart rate during exercise, it greatly reduces the work load of the heart. This raises the possibility that it will be particularly suitable in the treatment of hypertensive patients with angina pectoris, although definitive clinical studies have not yet been reported. Based on its hemodynamic effects, this drug should be better tolerated than pure beta blockers in hypertensive patients who have a very active life-style and who participate in endurance activities.

CONCLUSION

The major threat for patients with mild to moderate hypertension is sudden death, probably from ventricular fibrillation or myocardial infarction. Cerebrovascular hemorrhage is another important cause of death in hypertension. At present, it appears that all types of blood pressure reduction will reduce the risk of cerebral hemorrhage. Unfortunately, most studies to date have shown that antihypertensive therapy has no effect or only a modest effect on sudden death and myocardial infarction. However, a recent controlled study indicated that the beta blocker metoprolol was superior to diuretics in reducing heart attacks.^{32,33} The study has been criticized, and the results are still controversial.

Since no large controlled follow-up study has shown which type of drug will give the best prognosis, the first choice of an antihypertensive drug should be based on its pathophysiologic mode of action and side effects. Combination therapy and drugs with multiple actions, such as labetalol, seem to offer logical treatment for a large fraction of the hypertensive population. It is hoped that long-term results will indicate regression of cardiovascular damage, protection from complications, improved quality of life, and increased life expectancy.

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