DISCUSSION

In our study of adolescents with sustained hypertension, single-agent therapy with clonidine significantly reduced blood pressure and heart rate, while hydrochlorothiazide as a single agent significantly reduced only systolic pressure. After 24 weeks of therapy, 40 percent of the diuretic-treated group achieved the treatment goals vs 87 percent in the group treated with clonidine. No alteration of blood chemistry profiles was demonstrated in the clonidine-treated group, with significant hypokalemia occurring during hydrochlorothiazide therapy. Prior to treatment all participants had repeated blood pressure determinations above the 95th percentile for their age. Their average seated diastolic pressure was in the range of mild hypertension. However, it is possible that their relatively young age at the onset of fixed hypertension imposes a greater risk level. This concern is supported by recent reports demonstrating myocardial hypertrophy and altered myocardial function in mildly hypertensive adolescents. 7,8

The cardiovascular hyperresponsiveness to mental stress in these adolescents bears some resemblance to the hyperkinetic state of borderline hypertension. 9 Previous studies have demonstrated a form of impaired neurogenic activity in borderline hypertension. 10,11 The effect of the centrally acting agent clonidine on the mental stress response in this study was a reduction in diastolic pressure response and heart rate response to stress, with corresponding reduction in catecholamine levels. Catecholamine levels were higher during diuretic treatment. 4 Therefore, at this age and phase of hypertension, blood pressure control may be more sensitive to the effects of a centrally acting agent.

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Clonidine Monotherapy in Mild Hypertension

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Elsewhere in this symposium, we have reported on the hormonal and hemodynamic effects of clonidine used as a sole therapeutic agent, as well as the role of clonidine monotherapy in treatment of hypertension in the elderly. This article presents a synthesis and review of the evolution of the concepts in favor of the use of clonidine monotherapy in patients with mild hypertension.

Clonidine in Hypertension; Historical Perspective

Pioneer studies in the late 1960s and early 1970s on the clinical use of clonidine in hypertension examined and demonstrated its potent antihypertensive action across the entire range of severity of hypertension. These studies did not selectively focus on the use of clonidine in mild hypertension despite evidence in favor of its considerable efficacy. Attitudes and opinions of the day on antihypertensive therapy, however, precluded serious consideration of the use of clonidine in mild hypertension.

Contemporary major clinical trials seeking to establish the benefits of drug treatment, namely: the Veterans Administration Cooperative Study and the United States Public Health Hospitals Study failed to demonstrate a decisive difference in the mortality and morbidity between the treated vs control subjects with mild hypertension. The general consensus therefore relegated the drug treatment of mild hypertension only to those identifiable at higher risk.

The impressive and irrefutable protection afforded by drug treatment of moderate-to-severe hypertension led to heavy and almost monolithic emphasis on the importance of compliance with drug therapy so long it was efficacious in lowering blood pressure to the virtual exclusion of considerations as to how long term drug therapy per se might influence the interplay of cardiovascular risk factors in a patient with hypertension. Whereas this approach is more than justified in moderate-to-severe hypertension, its indiscriminate extension to mild hypertension and consequent lack of a critical scrutiny has been unfortunate. This attitude on the part of the physician towards the drug treatment of mild hypertension, generally an asymptomatic phase of the disease, has singled out the symptomatic side effects of antihypertensive drugs as the sole or the major determinant for selection of a therapeutic regimen. Accordingly, the other characteristics of drugs with relatively predictable incidence of symptomatic side effects, such as centrally-acting inhibitors of sympathetic tone, were not fully explored as to their suitability for use in mild hypertension.

In the design of the clinical trials seeking to establish the benefits of drug therapy, the use of the step-care approach of sequentially adding preselected drugs until reduction of blood pressure is achieved is necessary. In view of the
overwhelming success of the VA Cooperative Study in the treatment of moderate to severe hypertension, the step-care approach was endorsed by the U.S. Joint National Committee for Treatment of Hypertension and indeed found well deserved and wide acceptance by physicians. A tacit extension of these concepts to drug therapy in mild hypertension, however, was almost by default in the early period since no convincing argument existed either in favor of monotherapy for mild hypertension or against the dictated conventional approach of always starting with a diuretic or a beta blocker and adding one or more of the antihypertensive drugs if the desired blood pressure reduction had not been achieved.

The early clinical use of clonidine earned an image for the drug that it should best be reserved as a late step in the schema of step-care therapy. Two major contributory factors were: 1) the wide range of clonidine's antihypertensive efficacy that included its use in malignant hypertension and severe hypertension with complications; 2) the early use of relatively large doses of clonidine in severe hypertension that occasionally resulted in a rapid and symptomatic return of blood pressure and plasma catecholamines to pretreatment levels if therapy was abruptly discontinued.

**CHANGING CONCEPTS IN TREATMENT OF MILD HYPERTENSION**

For the purpose of highlighting a comparison with current concepts, I have described here aspects of a general approach to antihypertensive therapy particularly as related to the use of clonidine in mild hypertension that were contemporary with the report on the results of the VA Cooperative Study. Since the important question of when to treat mild hypertension, the largest segment of the hypertensive population, was unresolved at the time, in the ensuing decade several large clinical trials seeking the answer were initiated around the globe. The results of the two major trials, the U.S. Hypertension Detection and Follow Up Program and the Australian Trial in Mild Hypertension appear to endorse the view that aggressive drug treatment of most if not all patients with mild hypertension is beneficial in terms of reducing associated morbidity and mortality. Controversy over the trial design and the interpretation of the results, however, has been sharp and continued. A detailed critique on the subject is outside the scope of this paper. For the purpose of the present discussion, we shall therefore assume that the decision to treat mild hypertension with drugs has already been made. Under these circumstances we shall attempt to summarize how the accumulating evidence in several areas during the past decade has forced an extensive revision in our concepts on the drug treatment of mild hypertension.

**CHOICE OF DRUGS FOR MILD HYPERTENSION**

Benefits of drug-induced reduction in moderate-to-severe hypertension are overwhelmingly greater than the risks associated with years of drug therapy. The same is not true for mild hypertension. The risk associated with untreated mild hypertension is qualitatively different from that with severe hypertension. The incidence of so-called pressure-dependent complications is small in mild hypertension and the predominant risk consists of a potentiation of atherosclerotic heart disease. On the other hand, drug treatment of mild hypertension has been shown to provide a significant measure of protection, albeit incomplete against pressure-dependent complications such as stroke, cardiac hypertrophy and congestive heart failure.

The effects of drug treatment on coronary artery disease have been conflicting. Only one study claims to show a significant reduction in fatal incidence of coronary artery disease with drug treatment of mild hypertension. The reported results did not include the effects of treatment on nonfatal coronary artery disease and the study has been widely criticized for lack of a proper control. In the Olso study on the treatment of mild hypertension, the treated group experienced more myocardial infarctions. The Australian trial and the VA Cooperative Study showed statistically nonsignificant trends of decrease in fatal and increase in nonfatal myocardial infarctions in treated patients.

The expected cardiovascular mortality reported by the society of actuaries is a positively correlated linear function of the levels of systolic, as well as diastolic blood pressures including the subnormal normotensive and the mild-to-moderate hypertensive range. Why then does not a pharmacologically-induced lowering of blood pressure in mild hypertension result in lowering the cardiovascular death rate? Two theoretic reasons have been offered. The first and the more obvious one is that reduction of blood pressure alone may not be sufficient to reverse existing atherosclerotic vascular disease, but also, unlike in the normal vascular system, may induce a reduction in optimal blood flow beyond stenotic lesions in regional segments of the circulation. The second reason that has gained increasing attention and support in recent years ascribes the lack of treatment benefits to the intrinsic effects of the therapeutic agents.

Let us now examine the traditional recommendation to start drug treatment of every patient with mild hypertension with a thiazide diuretic. Morgan et al. have shown an adverse effect of thiazide diuretics on cardiovascular mortality. The recently published results of a much larger and longer trial, the Multiple Risk Factor Intervention Trial, have endorsed this possibility. A more definitive comparison of diuretics and beta blockers on cardiovascular morbidity and mortality is being carried out in the ongoing medical research council trial on mild hypertension in Britain. Prolonged diuretic therapy in mild hypertension may unfavorably influence cardiovascular mortality through the potentiation of ventricular ectopic activity by hypokalemia, atherogenesis by hyperlipidemia, and thrombotic complications by volume contraction and hemoconcentration.

Beta blockers, although not symptom free, are well tolerated by many. Metabolic consequences of prolonged beta blockade include hyperlipidemia, an elevation of low and very low density lipoproteins, a reduction of high density lipoproteins, and hyperuricemia—changes that are identical with those reported after prolonged thiazide diuretic treatment. Theoretically, these metabolic consequences may detract from the well-known cardioprotective action of beta blockers. Furthermore, repeat hemodynamic studies after 5 years of beta blockade in patients with hypertension indicated that the fundamental hemodynamic abnormality in the hypertensive, namely: the elevated peripheral resistance, was not corrected and the blood pressure reduction is achieved at the cost of a maintained reduction in cardiac output.
output.

These considerations constitute the basis of persuasive arguments that additional drugs other than diuretics and beta blockers deserve a serious consideration for prolonged therapy of mild hypertension.

IN SUPPORT OF MONOTHERAPY

Choice of drugs for treatment of mild hypertension should, therefore, be made considering not only the symptomatic side effects likely to influence compliance, but also more importantly the longterm consequent hemodynamic and metabolic aberrations in otherwise asymptomatic patients with mild hypertension. If totally innocuous drugs were available, a contradiction in itself for all drugs are foreign chemicals to the body, a convincing case could be made today for lowering even the most mild of elevated blood pressures. Alternatively, longterm drug therapy so far as practical should be limited to monotherapy with the chosen drug so that the longterm consequences can be monitored in the individual patient and add to the larger body of experience in the future. We have elsewhere discussed in detail the merits of individualized therapy for mild hypertension rather than a step-care approach, a recipe for all that disregards the considerations discussed in this article.

CLONIDINE IN MILD HYPERTENSION

Clonidine therapy for mild hypertension, particularly in the elderly, should be initiated with doses as small as 0.05 mg twice a day. If goal blood pressure is not achieved and unacceptable side effects do not occur, the dose can be titrated to three times a day to a maximal daily dose of 0.9 to 1.2 mg, although most patients with mild hypertension should be controlled with lower doses. The side effects of drowsiness and dry mouth in many patients tend to subside with time and with encouragement from the physician. The following features of clonidine action justify its use.

With continued treatment:

1. Blood pressure reduction achieved during the acute period (1 week) is continued unabated during the chronic period (3 months) with the same dose of the drug.

2. There is no sodium retention, no change in measured intravascular volume, and no development of tolerance or pseudotolerance to the antihypertensive effect.

3. Unlike the classic sympathetic inhibitors and vasodilators, clonidine therefore is effective and can be used as monotherapy in hypertension in a manner similar to diuretics or beta blockers.

4. Cardiac and renal hemodynamics remain essentially unaltered. Cardiac output is unchanged despite significant bradycardia. Glomerular filtration rate and renal blood flow are unaltered.

5. Plasma renin activity shows insignificant changes, plasma catecholamines decline.

6. There are no changes in serum electrolytes, uric acid and in blood sugar.

These findings indicate a lack of hemodynamic and biochemical perturbations and a lack of renin-angiotensin-aldosterone stimulation during chronic therapy with clonidine. Clinical experience, our own and others, indicates that the functional elements of peripheral sympathetic nervous system mediating posture, exercise and sexual function are not significantly interfered with during longterm clonidine therapy.

These features recommend the drug be used as monotherapy in mild hypertension in all age groups, especially in the elderly and particularly if small doses are efficacious and well tolerated.

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The Effect of Intravenous Clonidine Hydrochloride on the Isolated Forearm Venous Segment in Heart Failure*

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The effects of intravenous (IV) clonidine (150 µg) on the isolated forearm venous segment of ten patients with heart failure were studied. Clonidine reduced pressure in the isolated venous segment of all patients (12.8 ± 2.1 to 10.6 ± 1.4 mm Hg, p < 0.005). In addition, IV clonidine decreased the pressor response to mental arithmetic (2.9 ± 0.3 mm Hg to 1.8 ± 0.3 mm Hg, p < 0.05), while the pressor response to deep breath was slightly enhanced (4.5 ± 0.8 mm Hg to 6.1 ± 0.7 mm Hg, p < 0.05).

An increase in venous tone occurs as part of the complex circulatory adjustment to heart failure and is partially due to the increase in sympathetic activity. Exaggerated reflex venoconstriction responses to exercise have been recorded in patients with heart failure, and venous tone has been shown to decrease following treatment. Drugs which produce a decrease in venous tone have been found to be beneficial.

We have previously reported that intravenous (IV) clonidine hydrochloride reduces heart rate, preload, and afterload in patients with failure. Clonidine stimulates central α-adrenoceptors with a subsequent reduction in sympathetic outflow and increased vagal tone. We have studied the effects of IV clonidine on the isolated forearm venous segment (IVS) to determine if the effects of clonidine on venous tone are mediated by the autonomic nervous system. Also, we examined the effect of IV clonidine on certain reflexes which influence venous tone to better characterize the action of clonidine in heart failure.

MATERIALS AND METHODS

After obtaining appropriate informed consent, ten patients (mean age, 54.4 ± 3.7 years; range, 27 to 69 years) with chronic heart failure due to hypertension, ischemic heart disease, or other types of cardiomyopathy were included in the study. Criteria for heart failure included compatible symptoms and signs (eg, dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, cardiac gallop rhythm, edema) and cardiac enlargement on chest roentgenogram. Patients with serious liver or renal disease or patients with atrioventricular conduction abnormalities were excluded. All patients stopped taking medication except for diuretics for 36 to 48 hours prior to the study. Patients were studied in the supine position; a 25-gauge needle (internal diameter, 0.5 mm) was inserted into a systemic vein and into an isolated forearm venous segment.

A forearm venous segment, 3 to 5 cm long and free from valves and tributaries, was selected. The absence of valves was tested by occluding and emptying of the venous segment distally and confirming that the segment remained collapsed. A 25-gauge needle was...