Age and Cardiovascular Response Adaptation
Determinants of an Antihypertensive Treatment Concept Primarily Based on Beta-Blockers and Calcium Entry Blockers

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SUMMARY The patient’s age has great impact on the development of hypertension, its duration, and severity. In patients with essential hypertension, sympathetic cardiovascular control changes from an early phase with increased beta-adrenoceptor-mediated responses, e.g., cardiac output and renin, into a later phase where these responses are blunted and alpha-adrenoceptor-mediated vasoconstriction prevails, associated with higher intracellular free sodium and calcium concentration. This pathophysiological view of essential hypertension has its corollary in the pharmacotherapeutic approach. Younger patients, who often have high renin levels, respond better to monotherapy with a beta-blocker or with a converting-enzyme inhibitor. Older patients, who often have low renin levels, respond less well to beta-blockers but particularly well to calcium entry blockers as an alternative to diuretics. Therefore, beta-blockers and calcium entry blockers form new cornerstones for antihypertensive treatment and strategy, with the potential of cardioprotection.

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KEY WORDS • renin • adrenoceptors • age • therapy • calcium entry blockers • beta-blockers • converting-enzyme inhibitors

A patient’s age has great impact on cardiovascular regulation in different developmental phases of essential hypertension and, therefore, inevitably on the responsiveness to different antihypertensive drugs. In younger age, in the early phase of hypertension, in offsprings of hypertensive patients, or individuals with borderline hypertension, cardiac output is increased and the activity of the renin-angiotensin system is elevated while peripheral and renal vascular resistance is normal although the blood pressure is elevated. With older age, when high blood pressure becomes established, cardiac output and renin return to normal, the latter being even suppressed; peripheral and renal resistance are elevated.

The final determinant of the smooth muscle contractile process and thereby elevated arteriolar resistance is the free intracellular calcium concentration. According to two currently favored theories, the increased intracellular calcium concentration is the result of elevated intracellular sodium concentration brought about by either a transmembranous sodium transport defect or a deficient humoral natriuretic factor. There is little doubt that sodium plays a role in the development of hypertension. But as attractive as the above theories may be, we favor the pathophysiological concept in which the sympathetic nervous system, via subtle elevation of epinephrine, stimulates the release of norepinephrine from sympathetic nerve endings, and the resulting adaptive postjunctional adrenoceptor-mediated responses then play a pivotal role.

Age and Adrenoceptor-Mediated Cardiovascular Response Adaptation

As shown in figure 1, increased preganglionic sympathetic activity results in enhanced epinephrine secretion while stimulation of the sympathoneural system results, via postganglionic activation of postjunctional beta-adrenoceptors, in elevated cardiac output and renin secretion and alpha₁ and alpha₂ adrenoceptor-mediated vasoconstriction. The peripheral vascular tone is thus determined by the interplay of beta-adrenoceptor-mediated (vasodilator) and alpha₁ and alpha₂ adrenoceptor-mediated (vasoconstrictor) effects. Beta-adrenoceptor-mediated renin secretion can be considered as the long endocrine arm of the sympathetic nervous system because it causes angiotensin II-mediated vasoconstriction, amplifies central and peripheral adrenergic effects, and via selective aldosterone stimulation induces distal tubular sodium retention and vol-
volume expansion. Since epinephrine is taken up into the postganglionic nerve ending, it may also act as a co-neurotransmitter.

In the early phase of essential hypertension, beta-adrenoceptor-mediated cardiovascular responses, i.e., heart rate, exercise tachycardia, and therefore cardiac output as well as plasma renin activity and renin responsiveness, have been found to be elevated. In the later phase of hypertension, beta-adrenoceptor-mediated effects tend to be blunted, and this phenomenon can hardly be separated from age-related receptor changes; exercise tachycardia and heart rate response to isoproterenol are reduced; plasma renin activity is normal or low and hypo-responsive to sympathetic stimuli; and peripheral vascular responses to beta-adrenoceptor stimulation with metoprolol and isoproterenol are diminished. The observed changes in beta-adrenoceptor-mediated effects do not seem to be due to a change in number or affinity of the receptors, as assessed by radioligand binding studies on human mononuclear leukocytes. In fact, higher beta-adrenoceptor binding capacity tended to be associated with relatively lower physiological responses to isoproterenol in hypertensive individuals. This tells with reduced cAMP production following in vitro isoproterenol stimulation in older individuals. Thus, an alteration distal to the beta-adrenoceptor at the coupling site seems to be responsible for the reduced function that occurs with older age and higher pressure.

Enhanced Alpha-Adrenoceptor and Calcium-Influx-Dependent Vasconstriction in Essential Hypertension

Alpha-adrenoceptor-mediated vasconstriction quantified as the response of forearm blood flow to intraarterial infusion of the selective alpha-adrenoceptor blocking agent, prazosin, is greater in patients with essential hypertension than normotensive subjects, while the response to the nonspecific vasodilator sodium nitroprusside is comparable. With older age or in the later phase of hypertension development, this alpha-adrenoceptor-mediated vasconstriction remains enhanced and becomes relatively more prominent as the beta-adrenoceptor-mediated vasodilating force decreases. It is conceivable that other receptor-operated and calcium-influx-dependent factors contribute to the vasoconstrictor mechanism. Thus, in most recent studies, a post-junctional alpha-2-adrenoceptor-mediated vasoconstrictor mechanism has been identified which is comparable to that produced via alpha-2-adrenoceptors. It remains an open question whether this alpha-2-adrenoceptor response, which is also coupled to the cyclase system, changes with age and higher pressure.

An enhanced calcium-influx-dependent vasconstriction in patients with essential hypertension was documented by infusion of different calcium entry blockers, i.e., verapamil and the dihydropyridine.
derivatives, nicardipine and nitrendipine. These effects were comparable to those observed following reperfusion after 10 minutes of arterial occlusion.22 Verapamil-induced vasodilation correlated directly with plasma epinephrine concentration and inversely with plasma renin activity and angiotensin II concentration.21

Younger Patients Respond Better to Beta-Blockers

Since age influences the state of renin secretion6 and since the renin level is related to the response to beta-blockers, a relationship may exist between the age of the patient and the antihypertensive effect of a beta-blocker. Such an age analysis is shown in figure 2, which includes 243 patients treated with different beta-blockers. Beta-blockers reduce diastolic blood pressure to ≤ 95 mm Hg (Korotkoff V) in 75% of patients under 40 years of age, 50% of those 40 to 59, and only 20% of those over 60. This age analysis confirms our first6 and subsequent reports as well as studies by other authors.24,25 A decreasing response to beta-blockers with age agrees with other investigations in which heart rate responses both to beta-adrenoceptor blockade with propranolol26 and to stimulation with isoproterenol26 were blunted with older age.

The relationship between the decrease in renin levels and the long-term reduction in blood pressure with beta-blockers, as well as similar renin-related blood pressure responses to the more selective inhibitors of the renin-angiotensin system,27,28 indicates that renin suppression plays a pivotal role in the antihypertensive action of beta-blockers. The following sequence of events for the mode of action of antihypertensive beta-blockade may be proposed. Acute beta-adrenoceptor blockade is followed by baroreflex-mediated stimulation of sympathetic activity, resulting in unopposed alpha-adrenoceptor-mediated vasoconstriction,29 which initially counters the vasodilating effect of renin suppression. Later, a fall in blood pressure occurs whenever the renin-angiotensin system is involved in the maintenance of the hypertension. This is probably largely due to reduced direct angiotensin vasoconstriction. Concomitant reduction of aldosterone secretion, resulting in sodium diuresis and reduced plasma volume, may also contribute to the delayed onset of antihypertensive action of the beta-blockers. Other contributory factors may be the decrease in indirect angiotensin amplification of alpha-adrenoceptor-mediated vasoconstriction, and possibly diminished central and peripheral prejunctional beta-adrenoceptor-mediated stimulation.30 It follows from this view on the mode of action of beta-blockers that not only the pharmacological action of the drug but also the cardiovascular reactivity of a particular patient co-determine the degree of antihypertensive response.

Older Patients Respond Better to Calcium Entry Blockers

In spite of the obvious potential of calcium entry blockers to reduce vascular resistance and despite early
reports of their blood pressure-lowering action.\textsuperscript{31,32} Anti-hypertensive effectiveness has not been recognized for about 2 decades. Over the last few years several studies have documented the long-term anti-hypertensive efficacy of verapamil\textsuperscript{33-37} and nifedipine.\textsuperscript{38-40} At about the same time, new concepts have evolved linking a derangement in transmembrane sodium and calcium transport to the pathogenesis of essential hypertension.\textsuperscript{41,42} Accordingly, intracellular free calcium concentration in human platelets was found to correlate closely with the height of blood pressure, and both can be corrected by calcium entry blockers (unpublished observation). Therefore, single dose systemic administration of verapamil and nifedipine results in a prompt fall in blood pressure in patients with hypertension, but no changes were observed in normotensive subjects.\textsuperscript{21,31,39}

The overall anti-hypertensive efficacy of verapamil was found to be comparable to that observed with beta-blockers or diuretics.\textsuperscript{43} However, whereas the response to verapamil was directly related to the patient's age (fig. 3) and paralleled that of diuretics, beta-blockers again proved to be more effective in the younger patients and those with a higher renin level. On the other hand, the poor anti-hypertensive response to verapamil in younger and high renin patients may be due to the sympathetic and renin-angiotensin systems reactively countering the drug-induced fall in blood pressure. Since the reactivity of the renin-angiotensin system is blunted in the older and low-renin patients, verapamil may exert its anti-hypertensive effect to a greater extent in these cases. The mode of action of calcium entry blockers is not only determined by the potent vasodilating effect but also by the degree of sympathetically mediated counterregulatory phenomena.\textsuperscript{44} An additional anti-hypertensive effect of calcium entry blockers may be due to a decrease in adrenal and vascular responsiveness to angiotensin II.\textsuperscript{45}

A recent analysis with nifedipine indicated that a similar age, and particularly pretreatment pressure, and renin-related response pattern emerges.\textsuperscript{40} Thus, the observations made with verapamil can probably also be extended to other calcium entry blockers. Although the selectivity of calcium entry blockers is far from being understood, in terms of anti-hypertensive efficacy there does not seem much to choose between the calcium entry blockers. It may well be that the type and severity of unwanted effects may determine the choice of a particular compound, given similar anti-hypertensive efficacy. In this respect verapamil often causes constipation, while with nifedipine and its analogs, headaches and fluid/sodium retention may be a problem; the latter, however, seem to be less prominent when nifedipine is combined with a beta-blocker.

Calcium entry blockers, because of their different response spectrum and mode of action, may form a suitable partner for beta-blockers in an anti-hypertensive treatment plan. At the same time, verapamil must be combined cautiously with beta-blockers because of their common depressing effects on cardiac pacemaker cells and prolongation of atrioventricular conduction\textsuperscript{46} which, when verapamil was added to beta-blockers intravenously, has occasionally been found to result in sinus arrest and atrioventricular block. However, no
such deleterious events have been reported to date with the combination of a betablocker with oral administration of verapamil.

Cardioprotection in Patients with Hypertension

Long-term administration of beta-blockers in patients after myocardial infarction (secondary prevention) shows that treatment with different beta-blockers reduces the incidence of reinfection and sudden death. Results of some retrospective analyses suggest that beta-blocker therapy may reduce the occurrence of the first myocardial infarction or of sudden death (primary prevention). All these considerations strongly indicate the potential of beta-blockers to reduce cardiovascular risk in patients with or without silent coronary heart disease, e.g., in hypertensive patients. The proof of a primary prevention, however, can be expected only from prospective randomized or double-blind studies. Investigations, with the objective of determining whether the incidence of myocardial infarction and sudden death will be influenced by the inclusion of a beta-blocker in an antihypertensive treatment program compared with one which does not contain a beta-blocker, are currently in progress in an international prospective study including more than 6000 patients.

If calcium entry blockers can be established as the second cornerstone of antihypertensive therapy, they may also offer the prospect of a specific cardioprotective action by antagonizing the increase in myocardial calcium influx induced by sympathetic stimulation or electrolyte imbalance. Calcium entry blockers also appear preferable to diuretic agents, as the latter induce depletion of magnesium ("the endogenous calcium antagonists") and potassium. Use of diuretics in more severe forms of hypertension, and the associated potassium depletion with cardiac electrical instability, has been blamed for the observed excess cardiac mortality. On this basis, an alternative treatment plan for the future may be proposed (fig. 4) in which beta-blockers and calcium antagonists may complement each other: while a beta-blocker (or perhaps a converting-enzyme inhibitor) is used as the first line drug for the younger and high renin patients, a calcium antagonist may be the first choice for the older and low renin patients, to a large extent in place of a diuretic. This concept does not devalue the usefulness of diuretics, but it may change the order to their use in a treatment plan that is oriented towards the reduction of the higher incidence of myocardial infarction and sudden death in hypertensive patients.

References

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Discussion

DISCUSSANTS: R. AGABITI
F. BUHLER
G. MACGREGOR

AGABITI: You have shown, as Dr. Cody did this morning, that the antihypertensive effect of a calcium antagonist is inversely related to plasma renin activity. It was also shown by Dr. Lund-Johansen this morning that the antihypertensive effect of these drugs is related to peripheral resistance. If this is true, it means that patients with low renin are more vasoconstricted than those with high renin activities. Can you comment, please?

BUHLER: There are probably two components that determine the blood-pressure-lowering effect of calcium antagonists. Calcium antagonists, via calcium entry blockade, reduce intra-cellular free calcium and thereby peripheral arteriolar tone. In addition to the arteriolar effect, the degree to which pressure falls is determined by counterregulatory reflex mechanisms, such as adrenoceptor-mediated responses, or baroreflex sensitivity. Therefore, it is the older patients with blunted adrenoceptor-mediated effects who respond best to calcium antagonists.

AGABITI: Do you think that the antihypertensive effect of calcium antagonists is related to basal vasoconstriction?

BUHLER: There is a relationship between control of pressure and antihypertensive efficacy, as Dr. MacGregor has also shown.

MACGREGOR: If you do a multiple regression analysis as we have done on our data, which are very similar to yours, you find that the best predictor of blood pressure response is the pretreatment blood pressure. Renin and age, although related individually, lose their effect when you do multiple regression analyses. So there is obviously a complex relationship between blood pressure, age, and renin. Second, do you really need to use a diuretic with a calcium antagonist?

BUHLER: In one set of data, age was a stronger factor than control blood pressure, but in another, control blood pressure was a stronger determinant. A sample of some 40 to 60 patients may not be big enough a sample to unravel these interrelated or confounding factors.

To your second point, I am not saying that we do not need diuretics; in fact, I am convinced we do. The question is how and in what dose. Calcium antagonists will replace diuretics to some degree. When a calcium antagonist is combined with a diuretic, there may be some but not much more antihypertensive response. This again is a question of diuretic dose, which should be kept as small as possible.
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