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Scientific Update™

Hypertension and the Elderly

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Long-term treatment of hypertension is associated with significant reduction of mortality from cerebrovascular and, to a lesser degree, coronary artery disease. The relationship between hypertension control and cardiovascular mortality is discussed in this update along with specific issues of antihypertensive therapy in the elderly and inner-city minorities. The need for further trials with newer antihypertensive therapy is also identified.

Hypertension: burden of disease

Increased mortality from hypertension is related to organ damage – principally brain, heart, vasculature, and kidneys. A reproducible and widely accepted observation is that antihypertensive therapy reduces death from stroke by approximately 45%.[1-3] However, reduction in mortality from coronary heart disease is only 14%, resulting in controversy that antihypertensive therapy does not reduce death from myocardial infarction.[4] In this regard, it is important to realize that the reduction in coronary heart disease is highly significant ($p<0.001$). Moreover, the benefit is likely greater since in the earlier trials, coronary heart disease (CHD) deaths included deaths from lethal arrhythmias, cardiac failure, unstable angina, and sudden death. Since the thiazide dose used in these trials was twice that currently recommended, it may have been associated with a greater incidence of hypokalemic and hypomagnesemic-induced fatal arrhythmias. For example, in the MRFIT trial, CHD deaths occurred at greater frequency in the special intervening group that received more vigorous and, presumably arrhythmogenic therapy.[5]

Left ventricular pressure and volume overload account for the majority of hypertrophy, but other trophic factors are participative. For example, diabetic patients, when matched for degree of blood pressure, have greater left ventricular mass than nondiabetic patients. Similarly, blood pressure matched obese patients, possibly because of greater blood volume, have greater left ventricular mass.

An undisputed fact is that uncontrolled hypertension increases cardiovascular morbidity and mortality and that controlled hypertension reduces cardiovascular morbidity and mortality. Although left ventricular hypertrophy is an independent risk factor for cardiovascular mortality and, although several types of antihypertensive drugs (beta-blockers, calcium antagonists and ACE inhibitors) have been demonstrated to reduce left ventricular hypertrophy, it has not been demonstrated that reduction in left ventricular hypertrophy by antihypertensive treatment reduces cardiovascular mortality. Thus the important question remains – does reducing LV mass with antihypertensive therapy reduce cardio-vascular events? Dr. Frolich expressed some concern that the components of hypertrophy – myocyte hypertrophy and interstitial fibrosis - may not be uniformly regressed by antihypertensive therapy and that regressing myocyte mass

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more than connective tissue may predispose the heart to failure, especially diastolic failure, where the amount of fibrosis is known to correlate with the severity of failure.

The optimal drug to attempt regression also remains controversial. ACE inhibitors, and potentially AT-1 receptor antagonist blockage of angiotensin-II offer theoretical antitrophic advantages. Also unknown is what pathophysiologic factors resulting from antihypertensive therapy are most beneficial: reducing myocardial mass, reducing the blood pressure, increasing coronary blood flow [absolute flow, standardized flow (ml/gm), or flow reserve], or anti-arrhythmic effects.

Observation of a "J-shaped" curve (cardiovascular mortality plotted against blood pressure) may imply that, at lower blood pressure, cardiovascular mortality may increase. However, not all trials of blood pressure have described a J-shaped relationship, e.g., the SAVE and SOLVD trials. Thus, an increase in cardiovascular mortality from lower blood pressure is somewhat controversial. The Hypertension Optimal Treatment (HOT) Study, currently underway, is designed to answer this question – what is the optimal level of diastolic blood pressure control – 90 mm Hg? 85 mm Hg? 80 mm Hg?

Control of hypertension and cardiovascular events

The 12-year MRFIT Trial of 361,662 patient-years revealed a progressive (not J-shaped) relationship of blood pressure to endpoints of coronary heart disease, stroke, and end-stage renal disease.[5] Thus, the conclusion was that the lower the blood pressure, the better.

J-shaped relationships have been described in the context of blood pressure control and coronary heart disease. D'Agostino et al examined the relationship of CHD mortality to blood pressure in patients with a history of myocardial infarction (MI). A "J"- or "U"- shaped relationship was seen among patients with a history of MI with respect to diastolic blood pressure. The nadir of the diastolic BP relationship was unclear. No J-shaped relationship was seen in non-prior MI patients. The J-shaped relationship of systolic blood pressure was less striking, where a nadir of approximately 120 mm Hg was seen. Cruickshank et al further investigated the relationship of blood pressure control to coronary heart disease in 900 patients divided into tertile by treated diastolic blood pressure. Death from myocardial infarction did exhibit a J- or U- shaped relationship. When divided into patients with and without prior infarction, this relationship was principally accounted for by the patients with prior myocardial infarction.

In summary, J-shaped curves are seen with diastolic blood pressure, with coronary heart disease outcomes, and mainly in sicker patients with prior myocardial infarction. Whether the J-shaped relationship represents cause or effect remains controversial. Prevailing, but largely unproved, recommendations for treatment goals of antihypertensive therapy are target diastolic blood pressure of 80 mm Hg and target systolic blood pressure of less than 140 mm Hg for patients who can tolerate these goals without side effects or complications.

Challenges of antihypertensive treatments in the elderly

Orthostatic hypotension is encountered with increasing frequency in older patients. The definition of orthostatic hypotension that was used was a greater than 20 mm Hg fall in blood pressure on standing at 3 minutes. The prevalence ranges from 5-30% among patients over age 65 years but depends heavily on the definition used and the cohort studied. The highest incidence of orthostatic hypotension is seen in frail elderly patients (>50%) in nursing homes. Pathophysiologic factors that are associated with orthostatic hypotension and believed to be participative include higher systolic blood pressure, reduced compliance of the great

Table 1

HYPOTENSION IN THE ELDERLY

Orthostatic hypotension	
Prolonged inactivity	Elderly patients prolonged admissions to hospital
Medications	vasodilators, antihypertensives, neuroleptics, diuretics, sinemet
CNS disease	Shy-Drager's, Parkinson's, peripheral neuropathies, diabetes mellitus, alcohol, amyloidosis
Postprandial hypotension	(patient does not need to be standing or sitting)
Volume depletion	(fluid or blood)

SYMPTOMS ASSOCIATED WITH ORTHOSTATIC HYPOTENSION

dizziness	TIAs
weakness	nausea
lightheadedness	disturbed speech
syncope	vision changes
falls	angina

blood vessels, impaired baro-receptor reflexes, and post-prandial shunting of blood to visceral vascular beds. Associations of orthostatic hypotension include dizziness, dizziness on standing, medication use (esp. anti-Parkinsonian treatment), time of day (before breakfast), lower body mass, and institutionalization. There is only fair correlation of symptoms with the presence/absence and degree of orthostatic hypotension.

In the Systolic Hypertension in the Elderly Trial (SHEP), patients were examined for orthostatic hypotension (defined as a greater than 20 mm Hg BP drop) at baseline.[6] At 1 minute, 10.4% of patients had orthostatic hypotension ; at 3 minutes, 12.0%. About 5.3% of patients exhibited orthostatic hypotension at both times. A total of 17.3% exhibited orthostatic hypotension at either or both times. Therefore, it appears that when seeking to detect orthostatic hypotension, BP should be recorded at both times.

Orthostatic hypotension appears to exhibit considerable intra- and interpatient variability. Orthostatic hypotension is most frequent after breakfast and least frequent following lunch. Orthostatic hypotension is most strongly associated with elevated systolic blood pressure and somewhat less so with antihypertensive medication. Elevated systolic blood pressure is associated with a rightward shift of the cerebral blood flow vs. arterial blood pressure relationship. Agedness may also be associated with such a shift. A fall in arterial pressure is more likely to cause cerebral underperfusion. Unpublished data from the SHEP study suggests that self-reported dizziness is more predictive of falls and hip fractures than is orthostatic hypotension at one or three minutes of standing.

Reluctance to treat elevated systolic hypertension in the presence of orthostatic hypotension was acknowledged. Nifedipine, metoprolol, and enalapril were stated to be associated with reduced incidence of orthostatic hypotension among patients with elevated systolic BP, but the use of thiazides and, especially, prazosin was associated with an increased incidence of orthostatic hypotension among such patients. It was suggested that judicious and carefully monitored treatment of systolic hypertension may reduce the incidence of orthostatic hypotension and that peripherally acting alpha- blockers should be avoided completely.

Post-prandial hypotension (PPH) (defined as fall in BP>20 mm Hg after a meal) occurs more often after warm vs. cool meals, carbohydrate-rich vs. carbohydrate-moderated meals, in standing > sitting > lying positions, and in patients with autonomic dysfunction. The pathogenesis is unknown, but increased blood flow to visceral beds (seen as increased flow in the superior mesenteric artery by Doppler exam), impaired sympathetic nervous system responses (less than average rise in norepinephrine levels), and impaired baroreceptor reflexes (less than average rise in heart rate) are believed to be contributory. Age-related depression of peripheral beta-adrenergic responses are normal, but there is usually no aged-related depression of peripheral alpha-mediated responses. A 75-gm carbohydrate test meal is sometimes given to detect PPH. No specific treatment of post-prandial hypotension appears to be effective. Avoidance of exacerbating factors is recommended: eat small and frequent meals, avoid alcohol, lay supine post-prandially, avoid BP-lowering medications following meals, avoid dialysis following meals, avoid concurrent volume depletion, avoid physical inactivity.

Clinical trials in hypertension control

A session focusing on clinical trials discussed a mix of topics. A historical perspective was presented that the golden era of hypertension trials from 1960-1980. Over 250,000 patient years among 47,000 patients were amassed. The main antihypertensive agents employed were diuretics and beta-blockers. Most trials detected stroke benefit, but many were too small to detect a coronary heart disease benefit. For example, the Veterans trial, which employed hydrochlorothiazide, reserpine with or without hydralazine, detected stroke and vascular death benefit.[7] Analyzed in combination, coronary heart disease benefits were probably detected. Over the next 2 decades, of the 1980's and 1990's, hypertension clinical trials were sparse in relation to the proliferation of new drug types and monitoring techniques. Currently, the US market for antihypertensive medications is worth USD $20 billion. Calcium antagonists and ACE inhibitors have been on the market for over 15 years, but there are no trials sufficient from which to draw conclusions about their effects on major cardiovascular endpoints.

The structure and goals of the WHO-ISH Trialists Collaboration was presented by Dr. Stephen MacMahon as a multicentre effort to renew clinical trials in the sphere of antihypertensive therapy. The rationale of this effort is to define the advantages and disadvantages of newer agents, such as ACE-inhibitors and calcium antagonists, that may confer modest, but important effects. The primary and secondary objectives of these prospective trials were presented. As many anticipated, differences are small; large patient populations are needed. Thirty-one trials are confirmed and one

is pending. About 197,000 patients are needed, for 885,000 patient-years follow-up that will involve 24,000 major cardiovascular events and 14,000 coronary heart disease events. To establish that an anticipated 15% difference is significant, over 1,000 events are needed. By 1999, 15 WHO-ISH trials will be completed and by, 2002, thirty-two will be completed.

The effect of blood pressure control on progression of hypertensive disease in minority inner-city populations

In the United States, African Americans account for 30% of the end-stage renal disease population, and 210,000 patients are on hemodialysis or have received kidney transplants. Among 787 patients studied in a Southern California endstage renal disease group, the relationship of mean arterial blood pressure to renal function was sought. Progressive renal damage was monitored by plotting the reciprocal of serum creatinine vs. mean arterial pressure in African American and Hispanic men and women, further stratified by age and mean arterial pressure at entry. Antihypertensive medications were heterogeneous - about 50% of patients received ACE inhibitors. Renal dysfunction progressed the most rapidly in middle-aged African American men, and among elderly Hispanic women. African American men with arterial pressure in the 103-111 mm Hg range experienced a stabilization in the rate of rise of serum creatinine. It was concluded that intensive antihypertensive strategies are effective in delaying progression of renal disease.

Antihypertensive therapy

Treatment of hypertension in the elderly presents additional challenges because concomitant illnesses and frequent side effects. Thus, effective lowering of blood pressure without significant adverse effects is particularly important. The efficacy of low-dose nifedipine GITS was studied in patients with mild to moderate essential hypertension. Nifedipine GITS 20 mg provides stable plasma levels over 24 hours. A total of 187 patients were randomized in a double-blinded manner to placebo or 20 mg daily of nifedipine GITS, then 24-hour ambulatory blood pressure measurements were analyzed. Diastolic blood pressure (8.6 mm Hg vs. 5.4 mm Hg; $p = 0.001$) and systolic pressure (9.3 mm Hg vs. 5.0 mm Hg; $p = 0.006$) were significantly more reduced in GITS patients as compared to placebo. Adverse events were similarly infrequent in GITS patients as in those receiving placebo. The authors concluded that nifedipine GITS was well tolerated and effective in patients with mild to moderate hypertension. These results may allow further flexibility in tailoring antihypertensive therapy in the elderly patient by providing efficacious blood pressure control with a very low side effect profile. This lack of adverse effects may be associated with improved compliance in this susceptible group of patients.

Summary

Management of hypertension in the elderly is a worthwhile goal because of reduction in cardiovascular morbidity and mortality. Unique challenges may be encountered, including orthostatic and postprandial hypotension. There continues to be a need for further studies (which are underway) for evaluation of efficacy and safety of commonly prescribed antihypertensives, such as calcium antagonists and ACE inhibitors.

The need for effective and well-tolerated antihypertensive medications will continue to increase given the general demographics of the aging population. Emphasis on safety and compliance in the aging population, which presents special challenges, will be key as evidence from long-term trials such as Syst-Eur, demonstrate benefits of treatment.

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