Single Risk Factor Intervention May Be Inadequate to Inhibit Atherosclerosis Progression When Hypertension and Hypercholesterolemia Coexist

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Approximately 25% of the US population has hypertension as defined by blood pressure levels equal to or greater than 140/90 mm Hg. A similar percentage has hypercholesterolemia with plasma cholesterol concentrations exceeding 240 mg/dl. In addition to their high prevalence, these two risk factors coexist in greater than expected frequency. Hypercholesterolemia occurs in approximately 40% of hypertensive individuals, and hypertension is present in 46% of hypercholesterolemic subjects. This high rate of coexistence is due in part to the increased prevalence of both risk factors in obese subjects. Genetic factors also appear to be involved: 12% of hypertensive subjects less than 60 years of age exhibit the syndrome of familial dyslipidemic hypertension. Furthermore, combined abnormalities in both risk factors can induce markedly increased rates of atherogenesis and all of the clinical complications of atherosclerosis. Despite these impressive statistics, limited information is available regarding the mechanisms by which hypercholesterolemia or hypertension, or both, cause atherosclerosis and whether modification of either or both of these risk factors will reduce atherosclerotic disease and its complications.

Several studies have been performed in animals to examine the effects of relatively large reductions of plasma cholesterol on the reversal of established atherosclerosis. The findings generally have indicated that the correction of hypercholesterolemia can cause almost complete reversal of early atherosclerotic disease, but with prolonged hypercholesterolemia leading to advanced atherosclerotic lesions, the benefits of therapy are much more modest. In the latter instance, lowering of plasma cholesterol for prolonged periods can lead to such changes as a decrease in arterial lipids, reduction in number of intimal macrophages and smooth muscle cells, decrease in intimal thickness, and increased size in diameter of the arterial lumen. However, no decrease in extracellular connective tissue content is apparent, and the "regressed" vessel is generally more fibrotic than in the pretreatment period. In addition, the arterial changes induced by cholesterol lowering in hypercholesterolemic monkeys may not be associated with hemodynamic improvement, as evidenced by the fact that vasodilator capacity may not be increased in the coronary arterial bed after prolonged lowering of plasma cholesterol.

Hypertension causes many of the abnormalities observed in response to hypercholesterolemia, including changes in endothelial structure and function, increased arterial permeability, stimulation of proliferation of endothelial cells and smooth muscle cells, accumulation of macrophages and smooth muscle cells in the intima, increased expression of a variety of growth factors, connective tissue accumulation, and reduction in endothelium-derived vasodilation. However, experimental studies on the effects of correction of hypertension on atherosclerosis are complicated by the fact that hypertension by itself does not promote experimental atherosclerosis unless plasma cholesterol levels are raised. In rats, prolonged control of hypertension was shown to cause reversal of some induced cellular abnormalities, although extracellular changes, including collagen deposition, were only minimally affected. In prior studies performed in small groups of monkeys with combined hypertension and hypercholesterolemia, lowering of blood pressure appeared to have very little effect on coronary atherosclerosis.

The studies by Xu et al reported in the current issue of this journal provide new data on the arterial effects of lowering plasma cholesterol in cholesterol-fed cynomolgus monkeys who had previously been made hypertensive by coarctation of the thoracic aorta. The investigators observed that despite marked reductions in plasma cholesterol caused by dietary intervention, coronary atherosclerosis actually increased in severity in the monkeys that were hypertensive. The failure of cholesterol lowering to arrest the further development of atherosclerosis or to cause a regression of arterial changes in the
presence of hypertension could be due to several factors. The 6-month period of cholesterol lowering may have been too brief to effect favorable changes; even in the normotensive monkeys, only modest changes in atherosclerosis were induced by removal of excess dietary cholesterol. Furthermore, the detrimental effects of hypertension on the arterial wall would be expected to continue unless blood pressure were lowered. Hypertension also acts as a potent promoter of atherogenesis in the presence of hypercholesterolemia, and even the mild hypercholesterolemia that persisted after dietary cholesterol withdrawal may have been sufficient to cause further enhancement of atherosclerotic disease in the hypertensive animals. Whatever the explanation, the current studies highlight the need for additional experimental studies involving interventions designed to control multiple risk factors.

In humans, several clinical trials have been performed over the past 3 decades on the effects of treatment of either hypertension or hypercholesterolemia on the development of cardiovascular complications. Antihypertensive therapy has been shown to reduce markedly the incidence of stroke and congestive heart failure, but the effects on the development of coronary heart disease have been modest at best. Treatment of hypercholesterolemia has generally caused a reduction in incidence of clinically significant CHD, but an effect on total mortality has not been clear-cut. Although the clinical trials on hypertension have usually excluded patients with severe hypercholesterolemia, and those on cholesterol lowering have excluded patients with moderate or severe hypertension, patients with milder abnormalities in these risk factors have not been eliminated. Failure to control associated abnormal risk factors could have affected the results of these clinical trials. Other than for the Multiple Risk Factor Intervention Trial, which failed to achieve much reduction in plasma cholesterol, no large-scale clinical trial has been performed to test the effects of control of both hypertension and hypercholesterolemia in patients with combined abnormalities. The feasibility of such a trial has been enhanced by the development of new and potent cholesterol lowering and antihypertensive drugs.

Despite impressive advances in their control, cardiovascular diseases remain the major cause of death in the United States. In addition, the annual cost related to cardiovascular diseases for 1987 alone was estimated at approximately $127 billion or more than 20% of total health care costs. Control of cardiovascular disease must remain a major national goal, and important questions need to be resolved with respect to the pathogenesis of atherosclerosis and the methods by which prevention or regression of atherosclerotic disease can be achieved. The spectacular advances in molecular and cellular biology and the development of new therapies and technologies provide exciting new opportunities for understanding the biology of the arterial wall and for developing new forms of therapy to prevent arterial injury. Important clinical questions also need to be addressed regarding the therapeutic goals of antihypertensive and hypocholesterolemic therapy, the optimal drugs to be used, the risk/benefit ratio of the drugs, and the long-term effects on cardiovascular disease of risk factor modification. Such clinical studies often will require large numbers of patients followed up for long periods and will be costly. However, the overwhelming need for such information would appear to justify the large expense.

References

Key Words • atherosclerosis • hypercholesterolemia • essential hypertension
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_Hypertension_. 1991;18:130-131
doi: 10.1161/01.HYP.18.2.130

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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