

## THE EFFECT OF ANTIHYPERTENSIVE DRUGS IN THE SUPPRESSION OF ATHEROSCLEROSIS

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### ABSTRACT

The present investigation was undertaken to evaluate the effect of antihypertensive drugs on aortic atherogenesis in hypercholesterolemic rabbits. In enalapril and nifedipine treated rabbits aortic atherosclerotic plaque involvement was significantly decreased ( $p < 0.01$  and  $p < 0.05$ , respectively) as compared to the control group. However, in hydrochlorothiazide treated rabbits aortic atherogenesis was marginally inhibited, whereas in clonidine treated rabbits it was similar to the control group. These results suggest that the inhibition of atherogenesis in enalapril and nifedipine treated rabbits is independent of hypercholesterolemia and may be relevant in the selection of antihypertensive drugs, provided their protective effect can be demonstrated in future clinical trials as well.

*MJIRI, Vol. 13, No. 2, 93-96, 1999*

**Keywords:** Antihypertensive drugs, Atherosclerosis, Hypercholesterolemia.

### INTRODUCTION

Atherosclerosis and its complications constitute a disease complex of major public health importance and, as a cause of myocardial and cerebral infarction, constitute the chief cause of death in industrialized societies. The incidence of atherosclerosis is correlated with age, male sex, cigarette smoking, obesity, diabetes, hypertension and hyperlipidemia. Although the actual mechanism by which hypertension aggravates atherosclerosis is not clearly known, the available evidence indicate that hypertension appears to induce a sequence of changes in connective tissue metabolism, smooth muscle cells, endothelial integrity, platelet function, lipid profile and changes pertaining to insulin and glucose metabolism which may be important in the genesis of

atherosclerosis in hypertensive subjects.<sup>1</sup> Hypertension is a long-term disorder, and one of the most perplexing problems in the management of hypertension is the adverse effect of antihypertensive drugs or their metabolites on the cardiovascular system. The effect may be small, but still blunt considerably the beneficial effect of blood pressure reduction.<sup>2</sup> The present investigation was undertaken to find out the possible influence of diuretics (hydrochlorothiazide), centrally acting alpha 2-adrenergic agonists (clonidine), calcium channel blockers (nifedipine) and angiotensin-converting enzyme inhibitors (enalapril) on the development of atherosclerosis in cholesterol-fed rabbits.

### MATERIAL AND METHODS

Fifty male New Zealand White rabbits aged 4 to 6 months weighing 1.5 to 2 kg were randomly selected. They were caged individually in five groups of 10 rabbits each, in

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**Table I. Serum triglyceride, HDL and total cholesterol levels (mg/dL) of control and drug-treated hypercholesterolemic rabbits.**

Experimental group (n= 10)	Total cholesterol	HDL cholesterol	Triglyceride
Control	1904±390	16.6±4.3	284±76
Hydrochlorothiazide	2062±475	15.8±5.1	450±53
Clonidine	2246±569	15.4±4.4	381±72
Nifedipine	1980±413	17.0±6.3	230±39
Enalapril	1880±411	17.5±5.5	208±37

Results are given as mean ±SD.

**Table II. Tissue cholesterol content (mg/g wet weight) of control and drug treated hypercholesterolemic rabbits.**

Experimental Group (n= 10)	Aortic cholesterol	Liver cholesterol	Adrenal gland cholesterol
Control	19.4±5.8	58.3±10.5	164.2±21.3
Hydrochlorothiazide	18.0±6.4	50.5±12.2	145.0±20.5
Clonidine	17.8±5.9	54.7±11.0	164.4±18.8
Nifedipine	12.8±4.2*	51.2±13.3	183.5±25.8
Enalapril	5.2±1.3**	59.9±14.5	150.0±17.5

Results are given as mean ±SD.

\* $p < 0.05$ , \*\* $p < 0.001$  (significantly lower as compared to control).

similar environmental conditions.

After one week of initial adaptation to rabbit chow diet, each rabbit was fed 100 g of atherogenic diet (500 mg cholesterol+99.5 g rabbit chow) daily for a period of 10 weeks. Simultaneously, each group (except control group) of rabbits received one of the following antihypertensive drugs orally: hydrochlorothiazide 2 mg/kg/d, clonidine 0.013 mg/kg/d, nifedipine 1 mg/kg/d, enalapril 1 mg/kg/d.

### Serum analysis

Blood samples were collected after overnight fasting for estimation of serum triglyceride, HDL and total cholesterol levels.

### In vitro study

Rabbits were sacrificed at the end of 10 weeks and the aorta, adrenal gland and liver tissue were removed. The aortic atherosclerotic plaque involvement was measured.<sup>3</sup>

The liver, adrenal gland and aortic tissue cholesterol content was also determined.

## RESULTS

The values of serum triglyceride, HDL and total cholesterol of control and drug treated groups are summarized in Table I. The results indicate that serum triglyceride, HDL and total cholesterol levels of control (284±76, 16.6±4.3, 1904±390 mg/dL, respectively) and drug treated groups were not significantly different.

As shown in Table II, the aortic tissue cholesterol content of enalapril and nifedipine treated groups were significantly ( $p < 0.001$  and  $p < 0.05$ , respectively) lowered as compared to the control group.

The liver and adrenal gland tissue cholesterol content of enalapril and nifedipine treated groups were similar to the control group. Tissue cholesterol content of

**Table III. Percent of aortic surface area covered by atherosclerotic plaque in control and drug treated hypercholesterolemic rabbits.**

Experimental group (n= 10)	Percent of aorta covered by atherosclerotic plaque
Control	33 ± 10
Hydrochlorothiazide	29 ± 12
Clonidine	33 ± 11
Nifedipine	22 ± 6*
Enalapril	8 ± 2**

Results are given as mean ± SD.

\* $p < 0.05$ , \*\* $p < 0.001$  (significantly lower as compared to control).

hydrochlorothiazide and clonidine treated groups were not significantly different from controls.

The average extent of aortic atherosclerotic plaque involvement in enalapril (8 ± 2%) and nifedipine (22 ± 6%) treated groups was significantly lower as compared to the control group (33 ± 10%). The aortic atherosclerotic plaque involvement in the hydrochlorothiazide treated group was reduced by 15.1% as compared to the control group but this difference did not reach statistical significance. However, in the clonidine treated group aortic atherosclerotic plaque involvement was similar to the control group.

## DISCUSSION

The most interesting and important finding of this investigation was the prevention of atherosclerosis development and cholesterol accumulation in the aorta of enalapril and nifedipine treated rabbits. However, these preventive effects were independent of any changes in the serum cholesterol level. The accumulation of cholesterol in the adrenal gland and liver tissue were not influenced by these drugs. In hydrochlorothiazide treated rabbits atherosclerotic involvement of the aorta was marginally inhibited, whereas in clonidine treated rabbits it was similar to the control group.

The exact mechanism responsible for the antiatherosclerotic effect of calcium channel blockers is not yet clear. Calcium channel blockers appear to decrease the intracellular calcium concentration in the arterial wall smooth muscle cells (SMC). Reduced SMC calcium may decrease mitosis, collagen production, SMC migration and proliferation.<sup>5,6</sup> Their anticalcinotic action and related pronounced effect on lipoprotein uptake and metabolism and prevention of noxious arterial calcium overload may also be identified as a possible vasoprotective mechanism.<sup>7,8</sup> Calcium channel blockers may inhibit platelet activation as well as inhibit certain platelet functions such as calcium-dependent processes of adhesion, aggregation and release of platelet factors, which contribute to atherogenesis.<sup>9-11</sup>

Several possible mechanisms may be proposed for the anti-atherogenic effect of angiotensin converting enzyme (ACE) inhibitors. ACE inhibitors, by inhibiting angiotensin II formation, could theoretically be beneficial to the vasculature. Angiotensin II may act as a trophic factor stimulating the growth of vascular smooth muscle and myocardial cells and may alter the extra-cellular matrix in the arterial wall.<sup>12,13</sup> Angiotensin II acts directly by stimulating the synthesis of new receptors for platelet derived growth factor (PDGF), thereby potentiating the mitogenic action of PDGF.<sup>14</sup> Mas proto-oncogen product is an angiotensin receptor with mitogenic activity, and inhibition of angiotensin II could decrease the mitogenic activity mediated by this receptor.<sup>15</sup> Furthermore, angiotensin II stimulates macrophage mediated oxidation of LDL secondary to cellular lipid peroxidation.<sup>16</sup> However, the inhibition of angiotensin II synthesis by ACE inhibitors may explain the observed anti-atherogenic activity of enalapril.

The inhibition of atherogenesis in enalapril and nifedipine treated animals may be relevant in selection of antihypertensive drug therapy, provided their protective effect can be demonstrated in future clinical trials as well.

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