Doxazosin, an α-1 Antagonist, Prevents Further Progression of the Advanced Atherosclerotic Lesion in Hypercholesterolemic Hamsters

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The aim of this study was to examine the effect of doxazosin (DOX) on the further progression and regression of the advanced atherosclerotic lesion in the hypercholesterolemic hamster. Thirty-six, male F_1B Golden Syrian hamsters, 10 weeks of age, were divided into 3 groups of 12 and fed a nonpurified hypercholesterolemic diet (HCD) containing 10% coconut oil and 0.1% cholesterol (wt/wt) for 9 months (HCD 9). One group of hamsters was euthanized at 9 months and their aortas were collected, fixed, and stored until analysis. The remaining hamsters were either maintained on the HCD for an additional 6 months (HCD 15) or fed the HCD plus 20 mg/kg/d DOX for the 6 months. At the end of the study (15 months), the DOX-treated hamsters had significantly lower plasma total cholesterol (TC) (−68%), low-density lipoprotein-cholesterol (LDL-C) (−73%), and triglycerides (TG) (−74%) compared with the HCD 15. The lumenal narrowing and intimal thickening atherosclerotic lesions were significantly less in the DOX-treated hamsters compared with the HCD 15 (−66% and −70%, respectively). These data suggest that DOX treatment prevents further progression of the advanced atherosclerotic lesion possibly by lowering plasma TC, LDL-C, and TG in hypercholesterolemic hamsters.

DURING THE earliest stages of atherosclerosis, mechanical and/or biochemical agents including elevated concentrations of plasma low-density lipoprotein-cholesterol (LDL-C) may alter endothelial cells in a way that results in accumulation of LDL-C and apolipoprotein B (apo B) in the subendothelial space.[1-3] Subsequently, an increased number of circulating monocytes may adhere to endothelial cells, migrate into the subendothelial space, become activated tissue macrophages, and bind and internalize native and oxidized LDL particles to become foam cells.[1,4-6] A significant accumulation of these cells beneath the endothelial lining may lead to intimal swelling and develop into a fatty streak, the earliest morphologically evident stage of the atherosclerotic lesion.[7,8] Activated platelets can also adhere to these endothelial cells, macrophages, smooth muscle cells, and exposed subendothelial connective tissue and increase the rate of cholesterol ester accumulation and accelerate the formation of foam cells.

Doxazosin (DOX), a selective α-1 adrenergic inhibitor, has been shown to reduce blood pressure and decrease plasma total cholesterol (TC), LDL-C, and triglycerides (TG) while either maintaining or raising high-density lipoprotein-cholesterol (HDL-C) in animals and hypertensive humans.[9-20] In addition, studies have also shown that DOX decreases platelet aggregation[21,22] and increases tissue plasminogen activator activity,[23,24] which further reduces cardiovascular disease (CVD) risk.

Previously, our laboratory has also shown that DOX reduces intimal foam cell numbers and cell size accompanied by significant reductions in plasma TC and LDL-C in the hypercholesterolemic hamster.[11,25] In these studies, the effects of DOX on plasma lipids and aortic fatty streak formation showed a dose-response reduction in both plasma LDL-C and aortic lipid lesion area. Because no studies examining the effect of DOX on the long-term development of atherosclerosis have been published, the aim of the present study was to investigate the effect of DOX on the progression of the atherosclerotic lesion to a more advanced stage in the hypercholesterolemic hamster.

MATERIALS AND METHODS

Experimental Design

Thirty-6 male F_1B Syrian Golden hamsters (BioBreeders, Fitchburg, MA), 10 weeks of age, were placed in individual hanging cages and fed rodent chow (PMI Feeds, St Louis, MO) for 1 week to acclimate them to the animal facility. Food and water were provided ad libitum. The hamsters were then divided into 3 groups of 12 and fed a nonpurified hypercholesterolemic diet (HCD) consisting of PMI rodent chow (#5001) supplemented with 10% coconut oil and 0.1% cholesterol (wt/wt) for 9 months to initiate and progress lesions (pretreatment period). A nonpurified, instead of a semipurified diet, was chosen because our previous work,[26] and that of others,[27] demonstrated that the former induces a lipoprotein profile similar to humans. At 9 months, 1 group of hamsters (HCD 9) was killed and their aortas were collected, fixed, and stored until analysis. The remaining hamsters were maintained on the HCD for an additional 6 months (HCD 15) or the HCD plus 20 mg/kg/d DOX. At the end of the study, the remaining hamsters were killed, and their aortas were collected, fixed, and stored until analysis. Animals were maintained in an environmentally controlled environment (23°C) on a 12/12 hour light/dark cycle. Plasma lipids and lipoprotein cholesterol concentrations were measured at 2, 4, 6, 9, 11,

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Table 1. Mean Plasma Lipid and Lipoprotein Cholesterol Concentrations After the 2 Dietary Treatment Periods (pre- and posttreatment)

Diet	TC	LDL-C	HDL-C	TG
HCD 9	18.5 ± 1.84	17.1 ± 2.31	1.76 ± 0.21	20.9 ± 6.27
HCD 15	22.6 ± 6.55	20.6 ± 6.10	1.97 ± 0.48	34.6 ± 13.6
DOX	7.2 ± 1.81*	5.5 ± 1.70*	1.66 ± 0.29	9.1 ± 3.30†

NOTE. Values represent mean ± SD, n = 12. Mean plasma measurements of 2, 4, 6, and 9 months for HCD 9 group and mean plasma measurements of 11 and 15 months for HCD 15 and DOX groups (mmol/L).

*DOX significantly different from HCD 9 and HCD 15 at $P < .05$.

†DOX significantly different from HCD 15 at $P < .05$.

and 15 months of the study. All hamsters were maintained in accordance with the guidelines of the Committee on Animals of the University of Massachusetts Lowell Research Foundation and the guidelines prepared by the Committee on Care in Use of Laboratory Animals Resources, National Research Council (DHEW publication no. 85-23, revised 1985).

Plasma Lipoprotein Cholesterol and TG Measurements

Fasted hamsters (12 hours) were anesthetized with CO_2/O_2 (50:50) gas, and blood was collected via the retro-orbital sinus into heparinized tubes. Plasma was harvested after centrifugation at 1,500 × *g* at room temperature for 20 minutes and plasma TC[28] and TG[29] concentrations were measured enzymatically. Plasma very–low-density lipoprotein (VLDL) and LDL-C was precipitated with phosphotungstate reagent,[30] and HDL-C was measured in the supernatant. The concentration of nonHDL-C was calculated as the difference between plasma TC and HDL-C.

Quantification of the Advanced Aortic Lesion

At the time of sacrifice, hamsters were anesthetized with an intraperitoneal (IP) injection (0.02 mL) sodium pentobarbital (5 mg/100 grams of body weight [gbw]), and aortic tissue was obtained for lesion analysis.[11] The right atrium was incised for outflow, and the circulatory system was flushed via the left ventricle for 1 minute with 10% phosphate-buffered formalin solution at room temperature under physiologic pressure. After 2 minutes, the right atrium was clamped shut, and fixation continued for an additional 25 minutes. The heart and thoracic aorta were removed and fixation completed by pinning the tissue at in situ length in fixative overnight. Aortas were opened longitudinally, pinned out in a petri dish, stained with Sudan black, and photographed with color 35 mm film along with a calibration ruler. The percent of total area involved with lesion was measured and calculated from the photographs.

Every 1 mm along the aortic arch and thoracic aorta, a 1-mm section of tissue was taken for histologic examination to determine lesion volume. The tissue was processed and embedded in paraffin and 8-μm sections were cut from every 1 mm piece of tissue. The sections were mounted on glass slides, stained with hemotoxylin and eosin, and photographed with 35 mm color film. Lesion volume was determined by measuring the area of the lesion in each of a series of sections and factoring in the distance between each area measurement.

To characterize the nature of the lesions, transmission electron microscopy was performed. First, a 1-mm long section through the lesion area of fixed tissue was rinsed and additionally fixed in 3% cacodylate-buffered glutaraldehyde (0.1 mol/L, pH 7.3). After rinsing with buffer, the tissue was further fixed with 1% osmium tetroxide in 0.1 mol/L cacodylate buffer. The sample was rinsed and dehydrated through a series of ethanol concentrations, infiltrated with Epon 812, and polymerized. The embedded tissues were trimmed, thin sectioned on a Reichert Ultracut E ultramicrotome (Microm GmbH, Germany), the sections mounted on copper grids and stained with uranyl acetate and lead citrate. Sections were then examined using a Hitachi H600 electron microscope (Micro-Tech Optical, Hudson, MA), and photographs were taken at both low and high magnifications. Electron micrographs were examined and the percent lesion narrowing was calculated.

Statistical Analysis

SigmaStat software (Jandel Scientific, San Rafael, CA) was used for all statistical evaluations. A 1-way analysis of variance (ANOVA) was used to analyze the data between the 3 groups for plasma lipid and lipoprotein cholesterol measurements and for aortic tissue analyses. When a statistical significance was observed, a Student-Newman-Keuls post hoc test was performed. The Pearson Product Moment method was used for determination of correlations. All values are expressed as mean ± SEM and statistical significance was set at $P < .05$.

RESULTS

Plasma lipoprotein cholesterol and TG measurements collected at 2, 4, 6, and 9 months of the pretreatment period were averaged, and the means for the HCD 9 group are shown in Table 1. After 9 months, there were no differences observed for plasma TC, LDL-C, HDL-C, and TG concentrations between the dietary treatments.

The plasma lipoprotein cholesterol and TG measurements that were collected at 11 and 15 months during the treatment period were averaged and are also shown in Table 1. After 6 months of treatment, the DOX-treated hamsters compared with the HCD 15, had significantly lower plasma TC (−68%, $P < .0001$), LDL-C (−73%, $P < .0001$), and TG (−74%, $P < .0001$) levels. No difference was observed for plasma HDL-C levels between the HCD 15 and the DOX-treated hamsters.

The DOX-treated hamsters also had significantly lower plasma TC (−57%, $P < .0001$), LDL-C (−64%, $P < .0001$), and TG (−47%, $P < .003$) levels compared with the HCD 9 hamsters, with no difference in plasma HDL-C. There were no differences for plasma lipids and lipoprotein cholesterol levels between the HCD 15 hamsters and the HCD 9 hamsters.

The morphometric data for the atherosclerotic lesions in the hamsters, are presented in Table 2. After 15 months of dietary treatment, the lumenal narrowing, intimal thickening, medial area, intimal/medial ratio of the advanced atherosclerotic lesion of the aortic arch was significantly less in the DOX-treated hamsters compared with the HCD 15 (−66%, $P < .0001$; −70%, $P < .005$; −21%, $P < .002$; and −61%, $P < .002$, respectively) (Table 2 and Fig 1). Also, the lumenal narrowing, intimal thickening, the medial area, and intimal/medial ratio of

Table 2. Atherosclerotic Lesion Measurements After 9 months on the HCD for the HCD 9 Group and Either an Additional 6 Months on the HCD for the HCD 15 Group or 6 Months of 20 mg/kg/d of DOX Treatment in Hypercholesterolemic Hamsters

Diet	Lumen (mm^2)	Intima (mm^2)	Media (mm^2)	Luminal/Medial	Intimal/Medial	Lumenal Narrowing (%)
HCD 9	1.25 ± 0.25	0.10 ± 0.05	0.43 ± 0.07	2.93 + 0.82	0.24 + 0.11	7.49 ± 3.50
HCD 15	1.54 ± 0.38	0.28 ± 0.17*	0.64 ± 0.10*	2.40 + 0.36	0.43 + 0.19*	14.2 ± 3.83*
DOX	1.60 ± 0.16	0.09 ± 0.05	0.50 ± 0.05	3.20 + 0.41†	0.17 + 0.09	4.79 ± 2.91

NOTE. Values represent mean ± SD, n = 12.
Abbreviations: HCD, hypercholesterolemic diet; DOX, doxazosin.
*HCD significantly different from HCD 9 and DOX at $P < .05$.
†DOX significantly different from HCD 15 at $P < .05$.

the nonadvanced atherosclerotic lesion of the aortic arch was significantly less in the HCD 9 compared with the advanced atherosclerotic lesion in the HCD 15 (−47%, $P < .006$; −65%,$P < .03$; −33%, $P < .0008$; and −45%, $P < .003$, respectively) (Table 2 and Fig 1). Also, the luminal/medial ratio of the advanced lesion was significantly greater in the DOX-treated hamsters compared with the HCD 15 (33%, $P < .02$). No differences were observed between the DOX-treated hamsters and the HCD 9 for lumenal narrowing, intimal thickening, medial area, luminal/medial ratio, and intimal/medial ratio, although the hamsters in the DOX treatment group showed a slight decrease on average of the lumenal narrowing by 36% compared with the HCD 9.

For the DOX-treated hamsters, significant correlations were observed between plasma TC and LDL-C and intimal thickening ($r = .70$, $P < .04$ and $r = .69$, $P < .04$) (Fig 2A) and media thickening ($r = .69$, $P < .05$ and $r = .69$, $P < .04$) (Fig 2B). Also, plasma LDL-C was correlated to percent narrowing and plasma TG was correlated to lumenal thickening, but not significantly ($r = .60$, $P < .09$ and $r = .60$, $P < .09$). There were no significant correlations between plasma lipid variables and lesion formation for the other treatment groups.

DISCUSSION

The results of the present study demonstrate that 6 months of DOX treatment significantly reduced plasma TC and LDL-C levels in hamsters fed a HCD compared with their respective pretreatment levels (initial 9 months of on the HCD) and to hamsters fed the same diet without DOX treatment for an additional 6 months. While decreases in plasma TC and LDL-C levels are associated with a reduced risk of coronary heart disease (CHD), no change in plasma HDL-C levels was also observed in the present study, thus producing a greater positive effect on the reduction of CHD risk by reducing the TC/HDL-C ratio.

Numerous mechanisms have been proposed to explain the effects of α1-receptor inhibitors on plasma lipid metabolism;[32] however, it appears that the multifaceted action of these compounds may produce beneficial results synergistically. Several studies[33-35] have demonstrated that DOX upregulates LDL receptor activity in vitro, which may partially underlie the reduction in plasma LDL-C levels observed in vivo. The upregulation of LDL receptor activity may result from several intracellular regulatory mechanisms, which are affected by DOX. Studies have shown that DOX produces a significant decrease in cholesterol synthesis in vitro.[36] Similar studies in hamsters[33] also demonstrated that DOX significantly suppressed hepatic hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase activity, which reduced hepatic cholesterol synthesis. The subsequent reduction in hepatic cholesterol levels may initiate a compensatory mechanism, which involves secondary upregulation of the activity of LDL receptors,[37] thereby reducing plasma LDL-C levels. Also, intestinal HMG-CoA reductase activity may be suppressed by DOX, suggesting that cholesterol balance in the intestinal epithelium is disturbed, possibly affecting cholesterol absorption.[38] A decrease in cholesterol absorption has been observed in previous studies.[12,39]

Although there are data from studies in humans,[18-20,40] nonhuman primates,[9,10,12] and rodents,[11,33] which demonstrate the lipid-lowering properties and the antiatherogenic properties[11,25] on the development of the early aortic lesion with DOX treatment, no studies examining the effect of DOX on the development of the advanced aortic lesion have been published. Thus, the objective of this study was to investigate the effect of DOX on lowering plasma lipoprotein cholesterol and the further progression of the advanced atherosclerotic lesion in hypercholesterolemic hamsters. Compared with hamsters fed only the HCD for 15 months, hamsters fed the DOX-supplemented diet had significantly less narrowing of the aortic lumen and medial and intimal thickening. The hamsters on the DOX treatment were not significantly different from the pretreatment hamsters.

An antiatherogenic effect of DOX has been previously observed,[11,25,41] which could have resulted, in part, from plasma cholesterol lowering, however this does not completely explain this effect. There are now several areas of evidence, which indicate that many fatty streaks, which principally involve macrophage-derived foam cells, evolve into fatty and more complex atherosclerotic lesions and plaques containing smooth muscle cells, macrophages, and platelets.[1] Activated platelets can attach to endothelial cells and macrophages and increase the rate of cholesterol ester accumulation and accelerate the formation and accumulation of foam cells. Because the atherosclerotic lesion of the hamster contains smooth muscle cells,[11] which have α1-receptors and a previous study in our laboratory showed DOX inhibited platelet aggregation in monkeys,[13] it is possible that the changes observed in the present study on the

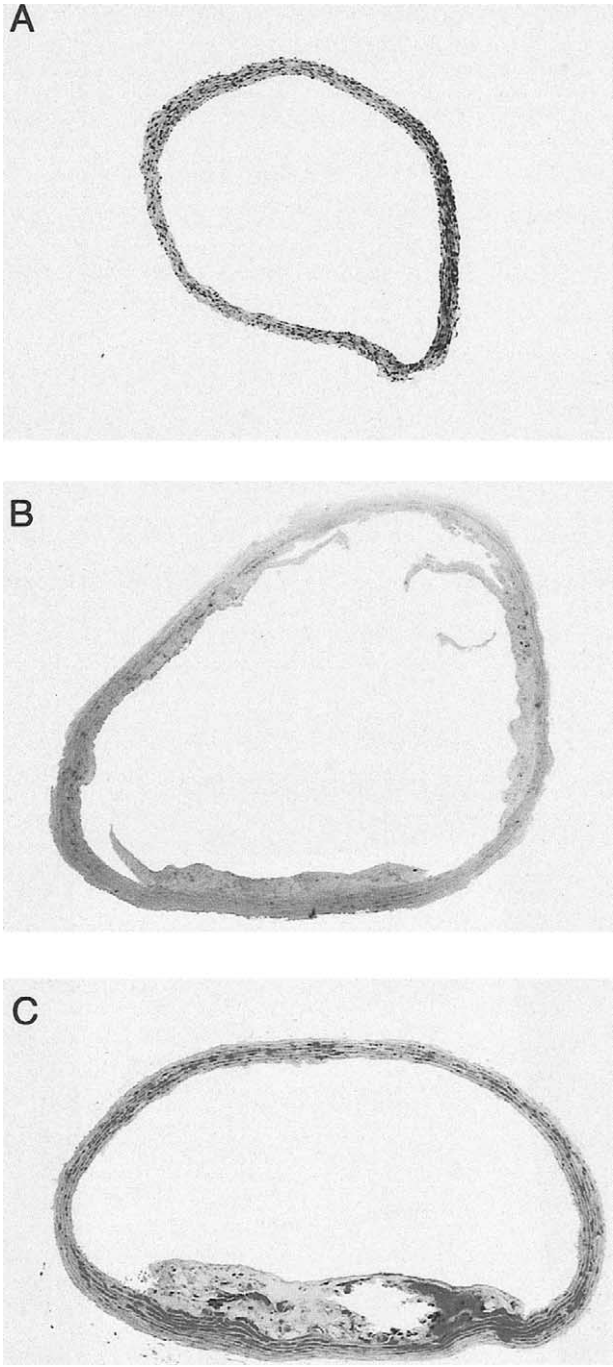

Fig 1. Aortas were opened longitudinally, stained with Sudan black, and photographed with color 35 mm film along with a calibration ruler. The percent of total area involved with lesion was measured and calculated from the photographs; 1-mm sections of tissue were taken for histologic examination to determine lesion volume. Lesion volume was determined by measuring the area of the lesion in each of a series of sections and factoring in the distance between each area measurement. To characterize the nature of the lesions, transmission electron microscopy was performed. The sections were mounted on copper grids and stained with uranyl acetate and lead citrate. Sections were then examined using a Hitachi H600 electron microscope, and photographs were taken at both low and high magnifications. Electron micrographs were examined and the % lesion narrowing was calculated. Aortic morphometric photomicrographs of representative hamsters from the (A) HCD 9 group showing very little narrowing of the artery after 9 months on the HCD, (B) the DOX group showing slight narrowing of the artery after 9 months on the HCD followed by 6 months of treatment with DOX, and (C) the HCD 15 group showing a well-developed lesion with narrowing of the artery after 15 months on the HCD.

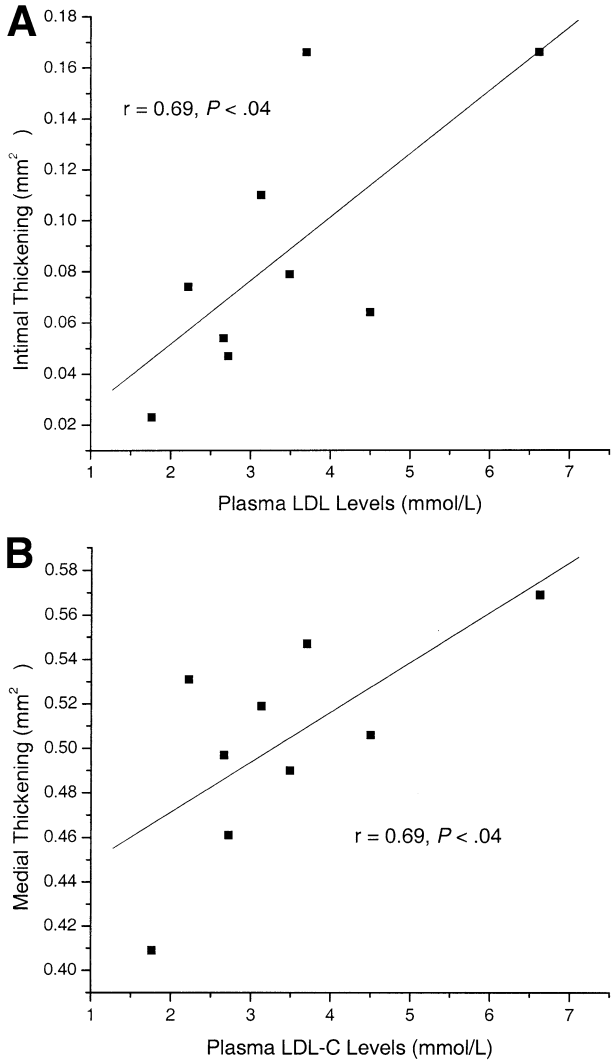

Fig 2. Correlations between plasma LDL-C levels and (A) aortic intimal thickening and plasma LDL-C levels and (B) aortic medial thickening for hamsters fed the HCD for 15 months and placed on 20 mg/kg/d of DOX treatment during the final 6 months.

arterial wall of the hamster aorta with DOX treatment reduced smooth muscle cell proliferation and increased platelet dissociation or decreased platelet aggregation within the arterial wall.

It is also possible that the antiatherogenic effect of DOX is due to its inhibition of collagen synthesis in the aortas, which

has been previously observed in rabbits[41] and rats.[42] Although chronically decreased blood pressure can also be responsible for decreased vascular collagen,[43] this is probably not an explanation, because earlier work[25] has shown that blood pressurereturns to normal with continuing administration of DOX in less than 6 weeks in hamsters.

In conclusion, it is evident from the present study that DOX is effective in preventing the formation of the advanced atherosclerotic lesion in hypercholesterolemic hamsters.

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