Effect of Cholesterol Atherosclerosis, Hypertension and Cortisone on Aortic Oxygen Consumption in Rabbit

By Edwin R. Fisher, M.D., and J. H. Geller, M.S.

There is an increasing number of studies suggesting that the aorta may play a significantly active role in the pathogenesis of atherosclerosis. The recognition of aortic synthesis of fatty acids, cholesterol, and phospholipids has led some investigators to disregard the more conventional concept of filtration or imbibition of plasma components. The studies of Briggs and associates, who noted that the aortas of rats were capable of oxidizing substances of the glycolytic and Krebs cycle, have provided further impetus to investigations relating metabolic activity of the aorta to the pathogenesis of this disorder. Indeed, Christie and Dahl observed the abdominal portion of the rat aorta respired less actively than the thoracic portion and that this discrepancy was most pronounced in aged rats and appeared more evident later in the life of females than males. They suggested a possible correlation of these findings with those observed in human atherosclerosis, particularly the lower oxygen consumption of the abdominal segment and the more frequent and severe atherosclerosis of this portion of the human aorta. It does appear germane to note, however, that atherosclerosis in the rat, similar to that observed in the rabbit but unlike that in the human, is most pronounced in the thoracic aortic segment.

Although the rabbit has been most widely utilized in investigations of experimental atherosclerosis, it is surprising to note that, aside from the excellent study of Dury and associates, no reference to oxygen consumption of the aorta in this species is evident.

They observed that aortic arch of the rabbit displayed greater oxygen consumption than that of the remainder of this structure. The administration of epinephrine, cortisone and growth hormone prior to sacrifice resulted in a decrease of activity of 13, 27 and 65 per cent respectively, in both segments studied. If interpolation of these results with the sites of predilection for atherosclerosis (after cholesterol feeding) in this species were made, one might conclude that such change is most pronounced in that portion associated with the greatest degree of oxygen consumption, notably the aortic arch.

Because of the paucity of studies concerning the respiratory activity of the aorta of the rabbit as well as the possible significance of such information in relation to the pathogenesis of atherosclerosis, it was considered worthwhile to study the \( Q_{O_2} \) of various segments of the normal rabbit as well as those of rabbits subjected to cholesterol feeding, renal hypertension, cortisone administration and combinations of these experimental states. The histological, histochemical and biochemical findings in these animals shall be reported in detail elsewhere.

Methods

Oxygen consumption was determined on portions of arch, thoracic and abdominal segments of aortas from 45 adult albino rabbits of both sexes and comparable ages by the standard Warburg manometric technic utilizing Krebs-Ringer's solution containing 1 per cent glucose. Readings were obtained at 15-minute intervals over a 90-minute period. After thermobarometric correction, the determinations were converted to milliliter oxygen per gram wet weight of aortic tissue. Aortas were obtained from 12 untreated rabbits maintained on a commercial diet and water ad libitum; 5 that received 2 per cent cholesterol within their diet; 5

From the Departments of Pathology, University of Pittsburgh and Veterans Administration Hospital, Pittsburgh, Pa.

Received for publication February 18, 1960.
that exhibited hypertension (115 to 160 mm. Hg), and 5 that received intramuscular injections of cortisone acetate (Cortone\textsuperscript{*}). In addition, the aortas from 4 cholesterol-fed rabbits with hypertension (110 to 145) 4 hypertensive, (120 to 140) cholesterol-fed animals receiving cortisone; and 6 that received cortisone as well as dietary supplements of cholesterol, as outlined above, were studied.

Hypertension was induced by the method of Page\textsuperscript{10} and blood pressure was measured by the ear capsule technic of Grant and Rothschild.\textsuperscript{11} Cortisone was administered daily for weekly periods alternating with similar time intervals during which no drug was given. The dosage employed was 5 mg./day during the first week, 10 mg./day during the third and 15 mg./day during the fifth, seventh and ninth weeks of the experiment.

All animals were sacrificed by the rapid intravenous injection of 2 ml. pentobarbital 60 to 65 days after the start of cholesterol feeding, cortisone treatment and/or induction of hypertension. Their aortas were quickly removed and washed in ice cold isotonic saline before and after the removal of adventitial adipose and connective tissue by blunt and sharp dissection. The aorta was then opened longitudinally and bisected so that one-half was available for the determination of QO\textsubscript{2} and the other for histological examination. Each was then separated into the following segments: arch (extending from immediately above the aortic valve to 1 cm. beyond the origin of the great vessels); thoracic (extending from the latter to the origin of the superior mesenteric artery); and abdominal (from the latter to the aortic bifurcation).

The degree of aortic atherosclerosis was graded as indicated in a previous report.\textsuperscript{12} Briefly, it consists of arbitrarily grading the degree of aortic atherosclerosis encountered in each segment as follows. Patchy lesions involving less than one-half of a segment without elevation were considered grade 1. Those involving half or less than half of the aortic segment but with elevated and frequently confluent plaques were considered grade 2. Those lesions considered as grade 3 were confluent, elevated and involved more than one-half of the segment.

Results

As indicated in table 1, aortic QO\textsubscript{2} of untreated control rabbits was greater in the arch and abdominal segments than in the thoracic portion. No statistically significant difference between the arch and abdominal aorta was evident. The thoracic segment consistently revealed the lowest QO\textsubscript{2} in all groups studied, regardless of whether respiratory activity was generally increased or decreased as compared to normal. Both cortisone administration and hypertension were associated with a marked increase of respiratory activity and their combination resulted in the greatest increase ob-

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*Merck & Co.

Circulation Research, Volume VIII, July 1960
served. Respiratory activity also was increased greatly in cortisone-treated, hypertensive rabbits with cholesterol atherosclerosis. In addition, activity was notably greater in the arch than it was in the abdominal portion, unlike the relative values obtained for these aortic segments in the control animals. On the other hand, a depression of respiratory activity was noted in rabbits with cholesterol atherosclerosis and those cortisone-treated animals also receiving a dietary supplement of cholesterol. The $Q_{O_2}$ could not be correlated with sex since too few animals were present in each group, although no difference was noted in the larger control group in which there were equal numbers of males and females.

The degree of aortic atherosclerosis was the greatest in hypertensive, cholesterol-fed rabbits. Atherosclerosis was negligible in cortisone treated, cholesterol fed rabbits, whereas that observed in cortisone-treated, hypertensive, cholesterol-fed rabbits was similar to that observed in normotensive, untreated, cholesterol-fed animals. Hypertension, cortisone or their combination failed to produce discernible macroscopic alterations within the aorta in animals not receiving cholesterol in their diet. No distinct correlation between the degree of aortic atherosclerosis and $Q_{O_2}$ or sex could be made for individual members of each group.

**Discussion**

Although our results indicate comparable degrees of respiratory activity for the arch and abdominal segment of the aorta of the normal rabbit, they do not essentially differ from those of Dury and associates who observed the greatest activity in the arch. It should be noted that these investigators compared the activity of the arch with that of the remainder of the aorta. Appropriate mathematical interpolation of our data into just 2 aortic segments (arch and remainder) also reveals the arch to possess a significantly greater degree of activity than the remainder of the aorta. Also, Dury and associates observed depression of $Q_{O_2}$ in rabbits receiving cortisone which is unlike our findings relating a marked elevation of oxygen consumption to the administration of this agent. However, it is to be noted that in their study only 1 injection of cortisone was given 4 to 6 hours prior to sacrifice which is not comparable to the prolonged cortisone treatment utilized in this study. The recognition that hypertension results in a marked increase in aortic $Q_{O_2}$ parallels the findings of Daly and Gurpide in rats with humoral and renal hypertension. They related this effect to an increase of the proportion of muscle cells to connective tissue fibers as well as greater intracellular activity attendant with the hypertensive state. Hypertrophy of the smooth muscle elements of the aortic wall in hypertensive animals in this study was not outstanding. However, an increase of aortic ground substance observed previously in the hypertensive rabbit was again observed in hypertensive animals in this study and may represent a morphological expression of increased activity on the part of cells responsible for its elaboration, notably aortic fibroblasts, and may represent a source of increased aortic respiration in the hypertensive state.

It is apparent that metabolic activity of the aorta may be profoundly altered by humoral agents as well as hypertension. Prolonged administration of cortisone markedly increased respiratory activity, and Briggs and associates observed alterations in aortic oxygen consumption of hyperthyroid and hypothyroid rats. Further, cortisone as well as hypertension resulted not only in an increase of $Q_{O_2}$ in all segments of the rabbit aortas examined, but differed from that in the normal with a pronounced elevation in the arch suggesting that these modalities may have a certain degree of selectivity.

Despite these effects on aortic metabolism, no consistent relationship could be detected between these alterations and the degree of atherosclerosis actually encountered or expected in cholesterol-fed rabbits subjected to such experimental procedures. Indeed, it is of interest that in the normal rabbit $Q_{O_2}$ was comparable in the arch and abdominal segments whereas atherosclerosis following cholesterol feeding was severe in the former.
and negligible in the latter. Similarly, although cortisone, like hypertension, was observed to increase aortic \( QO_2 \) cholesterol-fed animals receiving cortisone exhibited less atherosclerosis than untreated cholesterol-fed controls, whereas hypertensive animals fed cholesterol exhibited a greater degree of atherosclerosis than the latter. Although \( QO_2 \) was depressed or approximated the normal in the aortas from animals with established atherosclerosis following cholesterol feeding, similar values were obtained in cholesterol-fed cortisone-treated rabbits in which atherosclerosis was negligible. In addition, markedly increased values were observed in cortisone-treated animals without dietary supplements of cholesterol. This information does not necessarily minimize the role of aortic metabolism in the pathogenesis of atherosclerosis. However, it does indicate the necessity for the consideration of other factors, including those of the plasma, in the pathogenesis of this disorder in this species. It also suggests that the variations in metabolic activities reflected by the \( QO_2 \) need not necessarily be those primarily concerned with the pathogenesis of aortic atherosclerosis.

**Summary**

In vitro estimation of aortic \( QO_2 \) in normal rabbits revealed the thoracic portion to be lower than that of the arch and abdominal segments. These latter were not significantly different. Renal hypertension, cortisone administration and their combination with or without cholesterol feeding resulted in significant elevations of the oxygen consumption of all segments. The thoracic portion under these conditions was lowest and that of the arch was greater than that observed in the abdominal aorta. A depression of \( QO_2 \) was observed in the aortas from normotensive rabbits subjected to cholesterol feeding with or without cortisone treatment.

Although these findings indicate that hypertension and cortisone may profoundly alter the metabolic activity of the aorta, they could not be correlated with the degrees of cholesterol atherosclerosis observed in the various experimental situations explored.

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Circ Res. 1960;8:820-824
doi: 10.1161/01.RES.8.4.820

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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