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THE EFFECT OF BLOOD PRESSURE ON THE PASSAGE OF LABELED PLASMA ALBUMIN INTO CANINE AORTIC WALL

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According to one of the common theories (1, 2) of the genesis of atherosclerosis, that disease arises as a complication of the passage of plasma water and its solutes through arterial tissue. In this passage the plasma constituents are believed to move from the arterial lumen across the intimal endothelium and on through the arterial tissue. The low density lipoproteins are thought to share in this general movement of plasma constituents through arterial wall but to have characteristics that lead to their being trapped in the arterial intima where they decompose, leaving lipid deposits that eventually form atheromata. Because of this, it appears likely that information about the movement through arterial wall of plasma proteins, and especially of plasma lipoproteins, may increase our understanding of the genesis of atherosclerosis.

Studies of the movement of the lipoproteins into arterial wall have proved difficult to perform and interpret (3) because the lipoproteins contain both lipid and protein moieties and because their lipid components exchange freely between the various lipoproteins (4) and with the lipids of cells (5). It therefore seemed advantageous to develop information about the passage of a simple plasma protein like albumin through arterial wall because such studies are relatively easy to interpret and can be carried out relatively rapidly to form a background for the more involved study of the passage of lipoproteins into arterial tissue.

Our studies suggest that such a background will be pertinent. This conclusion is based on the similarities between the entrance rates of albumin into canine aortic wall, the entrance of labeled cholesterol into canine aortic wall, and the accumulation of cholesterol in canine aortic wall in experimental atherosclerosis. Albumin enters the inner layer of the aortic wall with a gradient of rates (6). The rate of entrance is fastest in the proximal aorta and becomes progressively less rapid down the length of the aorta. Labeled plasma cholesterol enters the aortic wall with a similar rate gradient (7). This similarity suggests that the plasma lipoproteins of the normal dog also enter aortic wall with a gradient of rates, but the lability of cholesterol as a label for lipoproteins renders such a conclusion tentative.

Early in the development of experimental canine atherosclerosis the accumulation of cholesterol in the inner layer of the aortic wall forms a gradient (8) similar to the gradient of the entrance rate of albumin. This suggests that some common factor is involved in the entrance of albumin and the accumulation of cholesterol, and is compatible with the hypothesis that low density lipoproteins enter aortic wall with a gradient of rates and thus give rise to the observed gradient of cholesterol concentrations. Alternative explanations are of course possible. In addition, the fact that later in the course of experimental canine atherosclerosis the gradient disappears and the concentration of cholesterol comes to be highest in the abdominal aorta makes the interpretation of the later course of the disease highly speculative.

Despite the foregoing qualifications, the observed similarities of the entrance rate of labeled albumin in normal dogs, the entrance rate of labeled cholesterol in normal dogs, and the rate of accumulation of cholesterol in dogs on an atherogenic regimen do suggest that information about the movement of albumin through arterial wall will provide a pertinent background to the study of the movement of lipoproteins through that tissue.

Studies already carried out have shown the existence of the gradient of rates and have demonstrated that the gradient is not due to the pulsatile nature of blood pressure or flow, since it is partially preserved *in vitro* under static conditions (9). The present paper reports studies

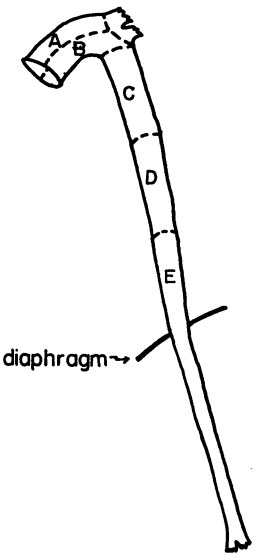

FIG. 1. THE SITES INTO WHICH EACH AORTA WAS DIVIDED.

of the effect of hypertension on the entrance of albumin into canine aortic wall.

PROCEDURE

The accumulation of labeled albumin and labeled erythrocytes in the aortic wall and skin of living dogs with normal or elevated blood pressure was measured. Similar studies were carried out on aortas removed from the body and filled with plasma under normal or elevated pressure. The blood pressure of all the dogs studied was measured with a mercury manometer through a needle inserted into the femoral artery.

Canine erythrocytes, labeled with radioactive chromium in the form of sodium chromate (10), were injected intravenously into ten normal dogs. Five were killed 30 seconds and five 1 hour after injection. Just prior to sacrifice, an arterial blood sample was drawn from each dog. The aorta of each dog was divided into the sites shown in Figure 1. The aorta from the valve ring to the brachiocephalic artery was separated into the outer side and the inner side of the arch. These were called sites A and B, respectively. The upper third of the descending thoracic aorta was called site C and the middle third, site D. The lower third of the descending thoracic aorta and the abdominal aorta was called site E. Sites A through D correspond to the sites we earlier designated as sites 1 through 4 (6). Site E is the same as our previous sites 5 and 6. Actually, results for sites 5 and 6 were obtained experimentally and then combined arithmetically. This was done because the results for the inner layer at sites 5 and 6 were almost the same. At some times they were slightly larger at one site or the other. The first two sites were split into inner, middle, and outer layers. The remaining sites were split into inner and outer layers. The weight of each aortic specimen and the area of the intimal surface of each specimen were determined. A piece of skin was taken from the posterior surface of the thigh of each dog. The radioactivity of the blood and tissue specimens was determined with a well-type scintillation counter. The hematocrit of each dog was determined. From the radioactivity of blood and tissue, and the hematocrit, the radioactivity of the erythrocytes and the erythrocyte content of the tissues were determined.

Human serum albumin labeled with radioactive iodine (RISA, Abbott) was used. Since this albumin contains a small amount of material that rapidly liberates free iodide, each batch was injected into a dog that was exsanguinated the next day. Its plasma contained labeled albumin largely freed of the objectionable component. This plasma was dialyzed overnight in cellophane sacs before injection into the experimental dogs. Thirty seconds after this material was injected the plasma contained about 0.2 per cent dialyzable activity. This gradually rose to about 2 per cent at 2 and 4 days after injection. Labeled albumin was injected intravenously into 49 dogs with normal blood pressure. Ten were killed 30 seconds, seven 5 minutes, nine 10 minutes, seven 3 hours, four 6 hours, four 18 hours, four 2 days, and four 4 days after injection. Just before sacrifice arterial blood was withdrawn. The tissues were dissected as described above. The radioactivity of the plasma, that fraction of the radioactivity that was dialyzable through cellophane, and the radioactivity of the tissue specimens were determined in the well-type scintillation counter. A small part of the activity in the tissues was due to dialyzable activity which consisted largely of free iodide. The tissue:plasma ratio of free iodide is 0.8 for aorta and 0.6 for skin (6). The activity of the tissues due to dialyzable activity was calculated (6), and this was subtracted from the total activity of the tissue to give the activity due to labeled albumin. The labeled albumin per gram of tissue at each site was divided by the amount of labeled albumin per milliliter of plasma to give the tissue:plasma ratio. The concentration of labeled albumin in plasma was expressed as the fraction of the injected dose in 1 ml of plasma per kg of body weight.

Hypertension was produced in a series of dogs by cutting the carotid sinus depressor nerves and in some cases the vagi. In one group of hypertensive dogs the mean arterial pressure was maintained between 180 and 190 mm Hg (mean, 185). In another group it was maintained between 225 and 260 mm Hg (mean, 240). The dogs were studied immediately after the production of hypertension.

TABLE I

Thickness of aortic tissues in millimeters

Site	Inner	Middle	Outer	Total
A	0.27	0.59	1.16	2.02
B	0.28	0.52	1.08	1.88
C	0.29		1.23	1.52
D	0.27		0.84	1.11
E	0.26		0.56	0.82

Labeled erythrocytes were injected intravenously into six dogs with pressures in the 240 mm range. Three were killed 30 seconds and three 1 hour after injection. Their blood and tissue samples were treated as described above. Thirteen dogs with pressures in the 185 mm range were injected with labeled albumin. Four were killed 30 seconds, five 10 minutes, and four 3 hours after injection. Nine dogs with pressures in the 240 mm range were injected with labeled albumin. Four were killed 30 seconds and five 10 minutes after injection. Their sera and tissue samples were treated as described above. Dogs with pressures in the 240 mm range were not studied longer than 10 minutes because of the difficulty of maintaining that degree of hypertension.

The procedure for the study of the aorta *in vitro* was as follows. Each dog was anesthetized, exsanguinated, and killed. The vessels coming off the aorta were ligated. The heart and aorta were removed from the body. A glass cannula was inserted through a cut in the left ventricle and passed down into the aorta so that it extended just beyond the aortic valve. It was secured in this position by a ligature around the aorta. The aorta was filled with plasma containing labeled albumin or blood containing labeled erythrocytes. An air pump to increase the pressure to the desired level and a mercury manometer were connected to the cannula. The blood or plasma used in this preparation was drawn under oil to preserve its CO_2 content.

Eight aortas were filled with blood to which labeled erythrocytes had been added. Two were subjected to a pressure of 100 mm Hg for 30 seconds, two to 100 mm for 10 minutes, two to 240 mm for 30 seconds, and two

TABLE II

Erythrocyte content of aortic tissue *

Site	Inner	Middle	Outer
In vivo studies in dogs with normal blood pressure			
A	0.006	0.004	0.002
B	0.008	0.003	0.002
C	0.003		0.004
D	0.004		0.005
E	0.004		0.007
In vivo studies in dogs with high blood pressure			
A	0.005	0.003	0.003
B	0.007	0.004	0.003
C	0.003		0.004
D	0.003		0.005
E	0.006		0.008

* Average of results obtained at 30 seconds and 1 hour expressed as milliliters of erythrocytes per gram of tissue.

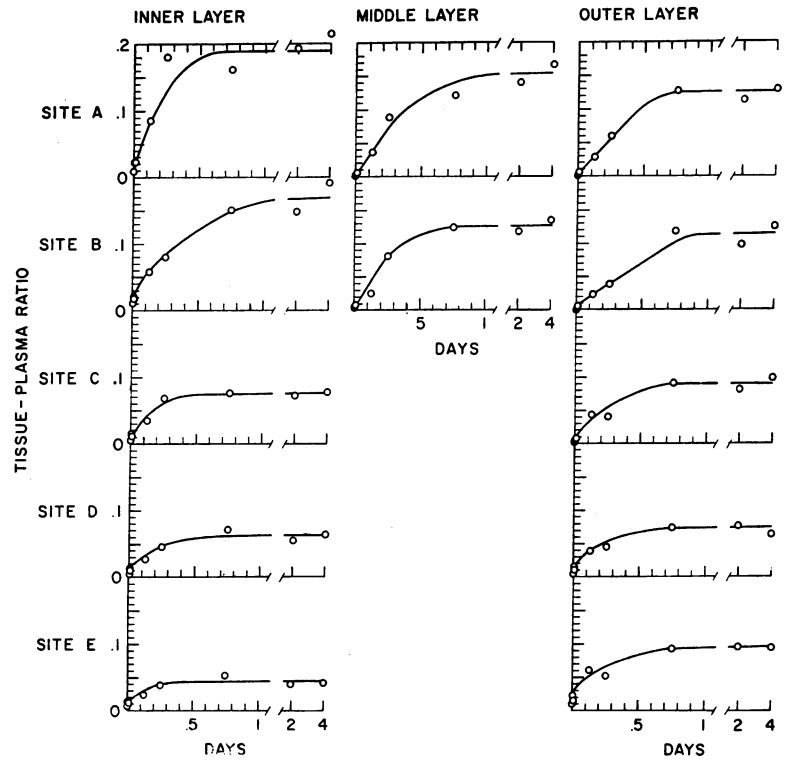

FIG. 2. THE RATIOS OF LABELED ALBUMIN IN THE LAYERS OF THE VARIOUS SITES OF THE AORTIC WALL TO PLASMA LABELED ALBUMIN PLOTTED AGAINST TIME.

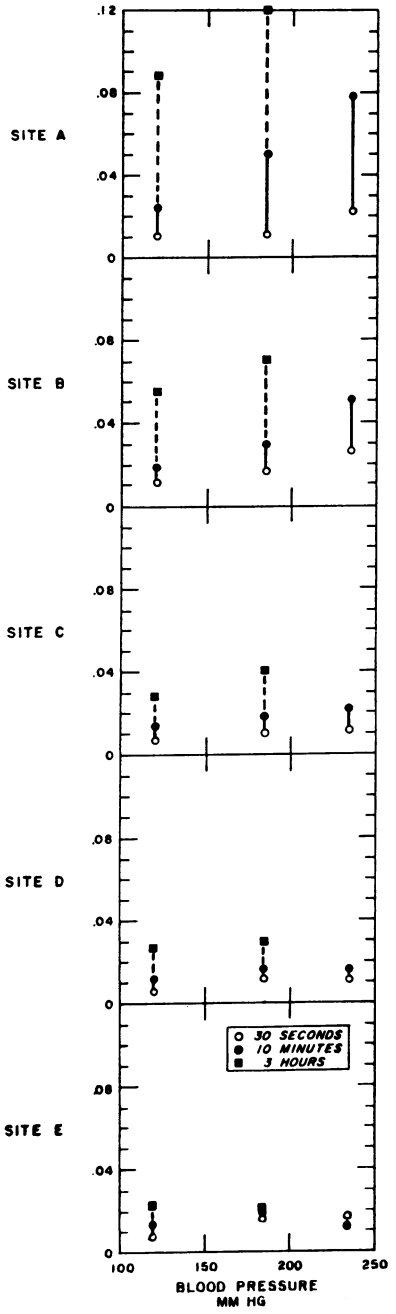

FIG. 3. THE EFFECT OF BLOOD PRESSURE ON THE TISSUE: PLASMA RATIOS AT THE VARIOUS SITES OF THE INNER AORTIC LAYER. The values at 30 seconds (○), 10 minutes (●), and 3 hours (■) after the intravenous injection of labeled albumin are shown.

to 240 mm for 10 minutes. The aortas and plasma samples were then treated as described above. Seventeen aortas were filled with plasma containing labeled albumin. Four were subjected to a pressure of 100 mm Hg for 30 seconds, four to 100 mm for 10 minutes, four to 240 mm for 30 seconds, and five to 240 mm for 10 minutes. The aortas and plasma samples were treated as described above.

RESULTS

Dogs with normal blood pressure. The mean arterial blood pressure in this group was 122 mm Hg. In Table I is given the thickness of the aortic layers of the dogs with normal pressure that were injected with labeled albumin. Thickness was computed as the quotient of weight and surface area. The thickness of the inner layer was about the same at all sites.

The erythrocyte content of each aortic division is shown in Table II. The values at 1 hour were no larger than those at 30 seconds after the injection. Therefore the ratios for the two times were averaged together for the table.

The time course of the tissue:plasma ratios of labeled albumin is plotted in Figure 2. The initial values for the inner layer are shown on a larger scale in Figure 3. From low initial values the ratios increased at first rapidly and then slowly until they finally became almost constant. The ratios increased most rapidly proximally and progressively less rapidly down the length of the aorta. The constant values finally reached were highest proximally and progressively less down the aorta.

In the proximal aorta where the ratio for the inner layer rose rapidly, the ratio for the outer layer rose more slowly than did that for the inner layer. In the distal aorta where the ratio for the inner layer rose slowly, the ratio for the outer layer rose more rapidly than did that for the inner layer.

An attempt was made to compute the rate of entrance of albumin into aortic tissue by an analysis using a single-compartmental model (11) that had previously been successfully applied to data that did not describe the early time course as well as do the present data (6). The present data did not fit the model satisfactorily. The experimentally determined tissue:plasma ratios rose more rapidly in the first 10 minutes after injection of the labeled albumin than did the ratios derived from the data by a least-squares analysis based on the model. For example, at site 1 of the inner layer the ratios observed from 30 seconds to 4 days were 0.010, 0.023, 0.024, 0.087, 0.181, 0.161,

0.193, and 0.214. The corresponding computed ratios were 0.014, 0.017, 0.020, 0.097, 0.149, 0.196, 0.194, and 0.194. An approximate F test of the goodness of fit of the data showed that the model could be rejected at the 0.1 per cent level at the site just described and at the 5 per cent level or better at most sites.

Because of the failure of the model to fit the data, a different type of analysis is necessary. Instead of using a more complex model, we will interpret the data without the explicit aid of a mathematical model. This is done by taking the tissue : plasma ratio due to extravascular albumin soon after injection as a measure of the rate of entrance of albumin. In order to compute the ratios due to extravascular albumin we have estimated the tissue : plasma ratios due to intravascular albumin. The ratios present 30 seconds after the injection of labeled albumin can be taken as adequate approximations of the ratios due to intravascular albumin if perfusion of the aortic tissue by the labeled albumin was complete by that time and if there was negligible penetration of the extravascular portion of the tissue by the labeled albumin in that time. Since the erythrocyte content of the aortic tissues was no greater at 1 hour than at 30 seconds after injection of labeled erythrocytes, perfusion of the aortic tissues by erythrocytes must have been complete by 30 seconds. It therefore appears probable that perfusion by plasma was also complete by that time. The following considerations suggest that there was little penetration of extravascular tissue by labeled albumin in the first 30 seconds after the injection. The average hematocrit computed from the tissue:plasma ratios was almost the same as the average central hematocrit determined on blood drawn from large vessels of the normotensive dogs in which studies were carried out with labeled erythrocytes. If there had been much penetration of extravascular aortic tissue by labeled albumin in the first 30 seconds after injection, then the true hematocrit of the blood in the aortic tissue would have had to be greater than the central hematocrit. This seems unlikely, since the hematocrit of the blood in most tissues is reported to be less than is the central hematocrit (12–14). We therefore reject the possibility that in the normotensive dogs there was much penetration of aortic tissue by labeled albumin in the first 30 seconds after injection. Thus, since there is evidence that perfusion of the aortic tissue by the labeled albumin was complete at 30 seconds and that penetration of the labeled albumin into the extravascular tissue was negligible at that time, the ratios at 30 seconds are taken as adequate approximations of those due to intravascular albumin.

The 30-second, tissue:plasma ratio subtracted from the ratio for a longer period after injection gives the ratio due to extravascular albumin. This ratio for an early time after injection is a measure of the rate of entrance of albumin into tissue, since the faster the entrance of albumin, the faster the tissue:plasma ratio rises. The tissue:plasma ratio is, of course, a function not only of the rate of entrance of albumin, but also of the rate at which albumin leaves the tissue and of the rate at which the serum concentration of labeled albumin falls.

The selection of the particular time at which the ratios will be considered as a measure of the entrance rate is influenced by two considerations. The first is that the earlier the time selected, the more the ratios depend on the entrance rate and the less they depend on the rate at which albumin leaves the tissue. From this standpoint, the earlier the time chosen the better. However, the accuracy of the data must be considered. The ratio of the concentration of extravascular albumin in the aortic tissue to the concentration in plasma is determined as the difference between the ratio at 30 seconds and the ratio at the subsequent time chosen. Very early in the course of the entrance of labeled albumin into the aortic wall, the ratio for extravascular albumin is determined as the difference between two relatively large numbers. The results are thus less reliable than those determined for later times. The most appropriate time for comparing the tissue:plasma ratios at the various sites varies with the experimental conditions. If the conditions are such that the ratios rise more rapidly than usual, then the ratios should be compared earlier than usual in their time course. The 3-hour ratios appear suitable for comparison of the entrance rates of albumin into the aorta of the normotensive dog. At this time they were small enough compared with the ratios eventually reached to assure that entrance was a more important determinant of the

ratios than was the exit. However, the ratios were large enough, compared with the 30-second ratios, to keep variation in the data from being troublesome. At 3 hours the ratios of extravascular albumin to plasma albumin for sites A through E of the inner layer were 0.077, 0.047, 0.029, 0.022, and 0.017. Thus this analysis, like the analysis by the single-compartmental model of less extensive data (6, 9), leads to the conclusion that labeled albumin enters the inner layer of the aorta with a gradient of rates.

The tissue:plasma ratios for the inner layer late in their time course showed the same gradient as they did early in the time course. This fact permits a limited inference about the rate of removal of labeled albumin from the aortic wall. In drawing this inference we define the rate of removal at time t as the fraction of the amount of labeled albumin in the aortic wall that is removed in unit time at time t. If the removal of labeled albumin from the distal aorta had been slow enough compared with its removal from the proximal aorta, the gradient in the late values would not have occurred. The limited inference that we can draw is that there was not a sufficient gradient in the rates of removal to prevent the occurrence of the observed gradient in the late values of the tissue:plasma ratios.

In the ascending aorta the tissue:plasma ratio for albumin rose faster in the inner layer than in the middle or outer layer. This observation, taken in conjunction with the virtual absence of capillaries in the inner layer (15, 16), indicates that albumin enters the inner layer of the ascending aorta directly across the intimal endothelium. The data do not exclude, of course, the possibility that albumin also enters the inner layer from the middle layer as well as across intimal endothelium. In the remainder of the aorta, the tissue:plasma ratio for albumin rose at approximately the same rates in the inner and outer layers, or more rapidly in the outer layer. Thus the ratios do not indicate whether in this portion of the aorta labeled albumin enters the inner layer across intimal endothelium, from the outer aortic layer, or by both these routes.

Dogs with high blood pressure. The thickness of the layers of the aortic sites was approximately the same in the hypertensive as in the normotensive dogs.

The erythrocyte content of each aortic division of the hypertensive dogs is given in Table II. The values at 1 hour were no larger than those at 30 seconds after the injection. Therefore the ratios for the two times were averaged together for the table. The erythrocyte content of the aortas of the hypertensive dogs was no greater than that of the normotensive dogs.

The 10-minute values for the concentration of labeled albumin in the plasma were about the same in the normotensive and the hypertensive dogs. The 3-hour values were somewhat lower in the hypertensive than in the normotensive dogs. The effect of blood pressure on the passage of albumin into the inner layer of the aortic wall is shown in Figure 3. At sites A, B, and C the tissue:plasma ratios at 30 seconds, 10 minutes, and 3 hours were higher in the hypertensive than in the normotensive dogs. The change owing to hypertension was large at site A, moderate at site B, and small at site C. Hypertension had no effect on the tissue:plasma ratios at sites D and E. The increases at sites A, B, and C were greater in the dogs with the more severe grade of hypertension.

Because of the rapidity with which albumin penetrated the aortic tissue of the hypertensive dogs, it seems appropriate to compare the 10-minute tissue:plasma ratios of the normotensive and hypertensive dogs. Since the plasma concentrations of labeled albumin were equal in these two groups at 10 minutes, we can conclude that there was no difference in the rapidity with which their plasma concentrations fell that might make interpretation of the ratios difficult. Because the erythrocyte content of the hypertensive dogs was the same as that of the normotensive dogs, we will assume that their intravascular albumin content was the same and will use the 30-second value from the normotensive dogs to compute the tissue:plasma ratios due to extravascular albumin for both groups. The 10-minute ratios due to extravascular albumin for sites A, B, and C were 0.014, 0.007, and 0.006 for the normotensive dogs, and 0.068, 0.039, and 0.016 for the dogs with the more severe grade of hypertension.

For statistical evaluation, we have grouped all the hypertensive dogs together and compared their tissue:plasma ratios at 10 minutes with those of the normotensive dogs at that time by means of the Behrens-Fisher test (17) for the difference

TABLE III

*Erythrocyte content of aortic tissue * from in vitro studies*

Site	Pressure: / Time:	100 mm Hg 30 sec	100 mm Hg 10 min	240 mm Hg 30 sec	240 mm Hg 10 min
A					
I†		0.002	0.004	0.004	0.002
M		0.001	0.002	0.001	0.002
O		0.001	0.007	0.004	0.007
B					
I		0.002	0.006	0.002	0.004
M		0.000	0.003	0.001	0.002
O		0.001	0.009	0.002	0.006
C					
I		0.001	0.002	0.002	0.002
O		0.001	0.005	0.001	0.003
D					
I		0.002	0.004	0.002	0.002
O		0.002	0.009	0.001	0.006
E					
I		0.002	0.010	0.002	0.006
O		0.006	0.027	0.005	0.020

* Expressed as milliliters of erythrocytes per gram of tissue.
† I is the inner, M the middle, and O the outer layer.

between means when the variances in the two populations may be unequal. The difference between hypertensive and normotensive dogs at site A was significant at less than the 1 per cent level, that at site B at less than the 5 per cent level, and that at site C at a little more than the 5 per cent level.

In vitro studies. The results obtained with labeled erythrocytes *in vitro* are shown in Table III. The results at 30 seconds did not differ greatly from those obtained in the living dog. However, in contrast to the results in the living dog, the erythrocyte content of the outer layer increased after 30 seconds. This was particularly striking at site E and at this site the erythrocyte content of the inner layer also increased.

The results obtained *in vitro* with labeled albumin are given in Tables IV and V. The values at 30 seconds, particularly those for the outer layer, were somewhat larger than in the living dog. At a pressure of 100 mm Hg there was little penetration of the inner layer by 10 minutes. No gradient of ratios was established. There was penetration into the outer layer particularly in the distal aorta. At a pressure of 240 mm Hg, there was marked penetration of labeled albumin into the aortic wall, and there was a striking gradient of ratios down the length of the aorta. The difference between the 10-minute ratios at a pressure of 240 mm Hg and those at a pressure of 100 mm Hg was significant by the Behrens-Fisher test at the 1 per cent level for site A and at the 5 per cent level at sites B, C, and D. The difference at site E was not significant. There was marked penetration of albumin into the outer layer.

TABLE IV

Ratio of labeled albumin in aorta to that in plasma 30 seconds after introduction of labeled albumin in studies in vitro

Site	100 mm Hg	240 mm Hg
A		
I	0.022	0.029
M	0.006	0.003
O	0.013	0.034
B		
I	0.033	0.022
M	0.006	0.004
O	0.011	0.021
C		
I	0.008	0.008
O	0.008	0.005
D		
I	0.007	0.007
O	0.014	0.026
E		
I	0.012	0.015
O	0.051	0.071

TABLE V

Ratio of extravascular labeled albumin in aorta to that in plasma 10 minutes after introduction of labeled albumin in studies in vitro*

Site	100 mm Hg	240 mm Hg
A		
I	0.005	0.068
M	0.000	0.037
O	0.011	0.043
B		
I	−0.008	0.077
M	0.001	0.032
O	0.010	0.048
C		
I	0.006	0.045
O	0.008	0.014
D		
I	0.005	0.022
O	0.022	0.066
E		
I	0.007	0.020
O	0.039	0.058

* This was computed as the difference between the ratios observed at 10 minutes and at 30 seconds.

Skin. The data on skin were collected to determine whether there was appreciable passage of albumin into skin during the first 10 minutes after injection. The 10-minute ratios did not differ significantly from the 30-second ratios. Thus there was no detectable penetration of albumin into the extravascular portion of the tissue during this first 10 minutes.

DISCUSSION

In previous work (6, 11) we used a single-compartmental model to interpret data on the movement of labeled albumin through many different tissues. In the present study on the aortic wall more accurate estimates of the labeled albumin on intimal endothelium and in the vasa vasorum have made possible the demonstration of a very rapid phase of entry that was not detected in the earlier studies. Because of this very rapid early phase of entry, the single-compartmental model does not fit the data, probably because the assumption of instantaneous mixing within the tissue is not an adequate approximation of the physical situation. Since the data on the movement of albumin into the skin do not show a rapid early phase of entry, the compartmental model remains an adequate description of those data.

In the living dog, elevation of the blood pressure caused a marked increase of entrance rate for the inner layer of the ascending aorta, a small increase for that layer of the upper descending thoracic aorta, and no increase for that layer of the more distal parts of the aorta. Elevation of the blood pressure *in vitro* increased the entrance rate for the inner layer along the entire length of the aorta. The increase was greatest proximally and progressively less down the length of the aorta. The cause of this difference between the results obtained *in vivo* and those obtained *in vitro* is not known.

However, one defect of the *in vitro* technique that may have contributed to this difference is demonstrated by the present experiments. The aortic content of erythrocytes in the outer layer increased *in vitro* with the passage of time. This was particularly marked in the distal aorta, and there the inner layer was also involved. This increase was probably due to dilatation or rupture of capillaries by the arterial pressure to which they were subjected in this type of static preparation. A continuation of this process of capillary damage probably led to the large ratios for albumin in the distal aorta observed in our previous *in vitro* study (9) in which the aorta was exposed to plasma under pressure for 3 hours.

The studies *in vitro* exclude the possibility that hypertension must be pulsatile to accelerate the passage of albumin into the aortic wall. This demonstration is important, because without it one could postulate that pulsatile movement of the aortic wall pumps lymph from it just as the movement of an extremity pumps lymph from that extremity, that this outward movement of lymph leads to an inward movement of water and albumin, and that in hypertension with an increased pulse pressure this process is increased. The experiment *in vitro* does not exclude this as a factor in the results but does show that it is not a necessary one.

However, even after the exclusion of mechanisms based on a pulsating pressure there remains a number of possible ways by which the increased pressure could have accelerated the movement of albumin into the proximal aortic wall. Increased lateral pressure could have caused an increased flow of water through the aortic wall. This water could have carried more albumin into the aortic

tissue and, by dilating porous channels in the intimal endothelium or in the aortic connective tissue, could have accelerated entrance by diffusion. On the other hand, the stretching of the aortic wall caused by hypertension could have altered the permeability of aortic endothelium or connective tissue so that albumin entered more rapidly by diffusion and convection. It appears probable that *in vitro* experiments separating the variables, stretching and pressure, will indicate whether pressure exerts its effect by stretching the aortic wall or in some other way.

SUMMARY

Labeled albumin enters the inner layer of canine aortic wall with a gradient of rates. It enters fastest proximally and progressively less rapidly down the length of the aorta.

Elevation of the blood pressure produces a marked increase in the entrance rate of labeled albumin into the inner layer of the ascending aorta, a small increase in the entrance rate into that layer of upper descending thoracic aorta, and no increase in the entrance rate into that layer in the more distal parts of the aorta. Thus hypertension makes the gradient of rates steeper.

Experiments *in vitro* exclude the pulsatile nature of the blood pressure as a necessary factor in the acceleration of the passage of albumin into aortic wall. The relative importance of hypertension per se and the associated aortic stretching cannot be assessed from these experiments.

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