The Interaction of Convection and Diffusion in the Transport of $^{131}$I-Albumin within the Media of the Rabbit Thoracic Aorta

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SUMMARY. The interaction of convection and diffusion in the transport of $^{131}$I-labeled albumin within the wall of rabbit thoracic aorta was studied in vessels excised at in vivo length. They were pressurized with a solution containing no tracer and immersed in a solution containing labeled albumin. The label then entered the wall tissue via the adventitia and had to diffuse against the convective flux which occurred from the lumen to the adventitia. Experiments were performed on intact and deendothelialized vessels pressurized to 70 and 180 mm Hg. At the end of each experiment the vessels were subjected to sequential frozen sectioning parallel to the lumenal surface. The radioactivity of the 20-$\mu$m-thick sections was determined and expressed as a tissue:labeled solution concentration ratio. Transmural profiles of these ratios were thus obtained. The steady state was found to be achieved by about 90 minutes. When the convection was enhanced by removal of the endothelium, the average ratios were lower than when the endothelium was intact, and the profile was much flatter. The results suggest that convection influenced macromolecular transport within the arterial wall, even in vessels with intact endothelium. (Circ Res 57: 856-863, 1985)

MATERIALS are transported through artery walls by both diffusive and convective mechanisms, but the relative roles of these processes in protein transport are still unclear (Swabb et al., 1974; Auvert et al., 1980; Caro et al., 1980a; Truskey et al., 1981). Uptake of $^{131}$I-albumin by the wall is enhanced by raising the transmural pressure (Duncan and Buck, 1961; Duncan et al., 1962; Auvert et al., 1980). Mechanisms proposed to account for this include increased fluid filtration and distension of the tissue. In an attempt to resolve these problems, studies were undertaken (Duncan et al., 1965; Fry, 1973) in which strips of artery were pressurized while being prevented from distending. The results of these experiments must now be considered inconclusive, because it has since been shown that compaction of the tissue can occur under such experimental conditions (Yamartino et al., 1974; Kenyon, 1979).

To reexamine the question of the interaction of convection and diffusion, we have filled excised, pressurized arteries with tracer-free physiological solution and incubated them in baths containing $^{131}$I-albumin. The tracer could thus diffuse into the tissue from the external surface while pressure-driven convection occurred in the opposite direction. The convective flow was varied by using intact and deendothelialized arteries, and the degree of distension was changed by studying arteries with normal cylindrical geometry at either 70 or 180 mm Hg transmural pressure. We have shown in a previous study that the filtration flow rate through the wall was enhanced by removing the endothelium and increasing the transmural pressure (Tedgui and Lever, 1984).

Information about the transport mechanisms was obtained by examining the spatial distribution of tracer within the wall after a steady state had been established.

Methods

Animal Preparation

Male New Zealand white rabbits (2–2.5 kg) were anesthetized by intravenous injection of 30 mg/kg sodium pentobarbital through the marginal ear vein. Each animal was artificially ventilated after tracheal intubation, and the sternum was split lengthwise. Heparin (1000 IU) was then administered intravenously, and the intercostal arteries were ligated on both sides of the aorta, 1–2 mm from their origins. The pleural membrane and surrounding fat were then carefully dissected away from the aorta. During the whole operation, the surface of the vessel was kept moist by application of Tyrode’s solution containing 2% albumin.

The aorta was ligated above the diaphragm. A 16-gauge needle pointing toward the heart was inserted just above this and was tied into the vessel. The needle was connected to a reservoir which was about 80 cm above the animal, and filled with Tyrode’s solution containing 4% albumin. The reservoir prevented depressurization of the aorta when a second ligature was placed on the aorta about 3 cm upstream of the first needle. A second needle pointing caudally and connected to a tap was then tied in the upstream end of the ligated segment. Both needles
then were clamped onto a rig which prevented the artery from shortening as it was excised. The vessel was finally immersed, while pressurized and held at in vivo length, in a bath containing Tyrode’s solution incorporating 2% albumin and 131I-albumin and maintained at 40°C. The vessel was flushed with Tyrode’s solution containing 4% albumin and Evans blue dye which served to indicate leaks and to test the integrity of the endothelium (Packham et al., 1967; Bell et al., 1974). The pressure within the vessel was controlled with a manometer connected to the upstream tap. Endothelial damage was minimized during the whole procedure by maintaining physiological pressure within the vessel and avoiding shortening. In about half the vessels, however, the endothelium was intentionally removed by inserting a snugly fitting silicone rubber tube into the aorta and rotating it during withdrawal. These vessels were then cannulated and excised in the same way.

Measurement of Filtration through the Wall

This procedure has been described in detail elsewhere (Tedgui and Lever, 1984). Filtration was measured by following the movement of a meniscus along a capillary tube interposed between the artery segment and the manometer which was used to maintain transmural pressure.

The integrity of the smooth muscle cells of the vessel wall at the coposition of some experiments was assessed by applying a solution containing angiotensin II (3 × 10−6 m) to the vessel. Marked vasoconstriction occurred, causing considerable reverse movement of the meniscus along the capillary.

Estimation of Radioactivity within the Wall

After incubation in the labeled solution, the artery was removed from the bath and then rapidly cut from the needles, opened axially, and divided into four segments of roughly equal area: two each from the dorsal and ventral regions. The segments were rinsed for 10 seconds in cold Tyrode’s solution, laid on a lightly greased microscope slide and rapidly frozen in a cryostat at −20°C. In cold Tyrode’s solution, labeled albumin and Evans blue dye which served to indicate leaks and to test the integrity of the endothelium (Packham et al., 1967; Bell et al., 1974). The pressure within the vessel was controlled with a manometer connected to the upstream tap. Endothelial damage was minimized during the whole procedure by maintaining physiological pressure within the vessel and avoiding shortening. In about half the vessels, however, the endothelium was intentionally removed by inserting a snugly fitting silicone rubber tube into the aorta and rotating it during withdrawal. These vessels were then cannulated and excised in the same way.

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since the average thickness of the section was found to be half of that of the subsequent sections.

To confirm this correction, a further series of four experiments was performed on deendothelialized arteries; because of their low $C_t/C_b$ values, the correction had been relatively larger in this group. At the end of incubation of these vessels, they were removed from the bath, and after brief rinsing they were immersed in 4% glutaraldehyde for 30 minutes before freezing and sectioning. In some unpublished studies on the uptake of iodinated albumin by the rabbit aorta in vivo, the distribution of label in the tissue after glutaraldehyde fixation in situ was comparable with that found in unfixed tissue. When labeled iodide was injected into rabbits and the arteries were fixed in the same way, the label was completely washed out of the wall. The concentration profiles across the fixed arteries in the present series were very similar to the corrected profiles found in the other experiments. Comparisons of the corrected $C_t/C_b$ values at each interval across the media with the corresponding values obtained after this fixation procedure gave no statistical differences.

**Results**

**Artery Structure**

The results of scanning electron microscopic and transmission electron microscopic studies of intact and deendothelialized aortas, fixed under 70 and 180 mm Hg, are presented in detail elsewhere (Tedgui and Lever, 1984). A completely intact layer of normal endothelial cells has been found on the vessels not subjected to silicone catheterization. In these arteries subjected to endothelial removal, the endothelial cells were damaged or absent. In both intact and deendothelialized arteries, the internal elastic lamella was intact and the underlying tissue appeared undamaged.

On some of the deendothelialized arteries in this study, we performed histoenzymic studies using Takeuchi's method (Takeuchi and Kiriaki, 1955). Phosphorylase activity in the smooth muscle cells of the inner, mid, and outer media, after 90 minutes of incubation at 70 and 180 mm Hg was similar to that found in control arteries freshly taken from an animal. Phosphorylase activity has been shown to be an early and significant index of arterial damage (Numano et al., 1973). These results suggest thus that the viability of the smooth muscle cells was maintained in the aortic preparation.

**Label Uptake Studies**

Twenty two arteries with intact endothelium and pressurized to 70 mm Hg were incubated in labeled solution for periods ranging from 15-180 minutes. The average $C_t/C_b$ profiles for each incubation time are shown in Figure 1. The increase in $C_t/C_b$ from zero with time at the lumenal boundary was possibly due to the accumulation of tracer in the lumenal solution, which increased with time.
Table 1

<table>
<thead>
<tr>
<th>x/L</th>
<th>t_w (min)</th>
<th>C'(90)/C_w'</th>
<th>C'(180)/C_w'</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2</td>
<td>32</td>
<td>0.87</td>
<td>0.98</td>
</tr>
<tr>
<td>0.3</td>
<td>31</td>
<td>0.89</td>
<td>0.96</td>
</tr>
<tr>
<td>0.4</td>
<td>27</td>
<td>0.89</td>
<td>1.0</td>
</tr>
<tr>
<td>0.5</td>
<td>28</td>
<td>0.89</td>
<td>1.0</td>
</tr>
<tr>
<td>0.6</td>
<td>26</td>
<td>0.91</td>
<td>0.99</td>
</tr>
<tr>
<td>0.7</td>
<td>32</td>
<td>0.87</td>
<td>0.93</td>
</tr>
<tr>
<td>0.8</td>
<td>31</td>
<td>0.89</td>
<td>0.94</td>
</tr>
<tr>
<td>0.9</td>
<td>27</td>
<td>0.91</td>
<td>0.97</td>
</tr>
<tr>
<td>1.0</td>
<td>28</td>
<td>0.89</td>
<td>0.95</td>
</tr>
</tbody>
</table>

* C'(90) and C'(180) represent the C_i/C_b values at 90 and 180 minutes, respectively. t_w and C_w' are the values obtained as the best-fit parameters of the equation C'(t) = C_w'[1 - exp(-t/Log 2/t_w)] to the experimental data.

In order to estimate the time required to achieve the steady state, the mean C_i/C_b values, obtained at each location across the wall, were plotted against time (Fig. 2). By the least-squares fitting of an exponential regression curve to the data, the times (t_1/2) when half the steady state concentration, C_w, was attained, were determined for each curve. The t_1/2 values at different locations ranged from 26–32 minutes. Thus, the C_i/C_b values obtained after 90 minutes represented 87–91% of C_w, and those obtained after 180 minutes represented 93–100% of C_w (Table 1). Since the C_i/C_b values for arteries incubated for 90 minutes were within 10% of C_w, it was assumed that 90 minutes was an adequate period to achieve a steady state.

To verify that 90 minutes were sufficient to achieve a steady state in deendothelialized arteries, experiments were run for 90 minutes on three of those arteries pressurized to 70 mm Hg and for 180 minutes on three additional deendothelialized vessels. At 90 minutes, the average C_i/C_b values at each interval across the wall were found to be within 10% of the corresponding values for arteries incubated for 180 minutes.

Of the five deendothelialized vessels pressurized to 180 mm Hg, three were incubated for 90 minutes and two for 180 minutes. In this series too, the average 90-minute C_i/C_b value at each interval across the wall was found to be within 10% of those at 180 minutes.

No complete time-course study was performed on arteries with intact endothelium and pressurized to 180 mm Hg. Four arteries were used under this experimental condition, and they were incubated for 90 minutes.

Figure 3 shows the profiles after 90 minutes of incubation of the relative Na^{131}I tissue concentration (C_i/C_b) in one aorta with and without endothelium at 70 and 180 mm Hg. Maximum values were found in the mid-media. At the end of the incubation period, the lumenal concentration in labeled iodide was found to be 25–35% of that in the external bath. This could account partly for the lumenal concentration gradient. The fall in concentration toward both the external and luminal surfaces might also be due to some loss of the low molecular weight molecules from both sides of tissue when it was rinsed in cold Tyrode’s solution for 10 seconds. In each experimental condition, the (C_i/C_b) values obtained at each location were used to correct the corresponding measured ^{131}I-albumin C_i/C_b values, as described above.

For each experimental condition, average steady C_i/C_b profiles were obtained by pooling data from 90- and 180-minute experiments. The profiles for both intact and deendothelialized arteries incubated at 70 and 180 mm Hg before and after correction for free iodide contamination are shown in Figure 3.
4. The presence of free iodide led to overestimates of \( ^{131}\text{I}-\text{albumin} \) uptake varying from 2% for the highest measured values of \( C_t/C_b \) to about 30% for the lowest.

The \( C_t/C_b \) values decreased nonlinearly from the external to the lumenal surfaces. The average \( C_t/C_b \) values were lower in deendothelialized arteries than in intact vessels. Furthermore, the \( C_t/C_b \) profile was much flatter in deendothelialized arteries pressurized to 180 mm Hg than in the other vessels.

In nine experiments, aliquots of the intraluminal solution were sampled at the end of the incubation. The activity of these depended on the incubation time, and averaged 0.23 ± 0.24% (varying between 0.03% and 0.6%) of that of the external solution. In six experiments, trichloroacetic acid (TCA) was used to precipitate protein-bound label from the lumenal solution. The average TCA-precipitable radioactivity was only 29 ± 6% of the total radioactivity, indicating that much of the intraluminal radioactivity was due to free iodide diffusing through the wall from the external bath.

**Discussion**

During the in situ preparation of the artery, some of the adventitia was removed with the pleural membrane and surrounding fat. The adventitial layer does not appear to contribute directly to the mechanical properties of the vascular wall (Wolsinsky and Glagov, 1964) and the histological appearance of the media is unchanged when the adventitia is removed (Wolsinsky and Daly, 1970; Tedgui and Lever, 1984). The transport properties of the media are therefore assumed to be unchanged when part of the adventitia is removed.

By assuming that the steady tracer concentration at the adventitial surface is the bath concentration, there may be some error because of the unstirred layer in the solution next to the outer surface (Dainty, 1963; Pedley and Fischbarg, 1978). The bath was not mechanically agitated, but because the upper surface was open to the atmosphere there would be appreciable convection within the solution. This factor, together with the convex curvature of the outer surface of the wall, suggests that the thickness of this unstirred layer is unlikely to exceed 100 μm (Wright et al., 1972).

If \( J_v \) is the velocity of the pressure driven water flow through the wall and \( D \) is the diffusion coefficient of tracer molecules in the external solution, then the concentration of tracer next to the wall \( C_m \) can be expressed (Dainty, 1963) as:

\[
C_m = C_b \cdot \exp \left( -\frac{J_v \cdot d}{D} \right)
\]

where \( d \) is the thickness of the unstirred layer (assumed to be 100 μm). The largest average value of the filtration was \( 9.5 \times 10^{-6} \text{ cm/sec} \) (Tedgui and Lever, 1984) and the free diffusion coefficient of albumin is \( 6.8 \times 10^{-7} \text{ cm/sec} \) (Wakeham et al., 1977) so the wall concentration is at least 87% of the bath concentration. The effects of the unstirred layer are therefore probably not responsible for the much lower concentration of tracer found in deendothelialized vessels at high pressure.

After the beginning of the experiment, when the tracer has started to enter the wall from the adventitial surface, the tracer flux within the wall \( (J_d) \) can be described as a combination of convection \( (J_c) \) due to bulk flow and permeation \( (J_p) \) due to diffusion (Kedem and Katchalsky, 1958). If the media is assumed to be a homogeneous membrane extending from \( x = 0 \) (the lumenal surface) to \( x = L \) (the adventitial surface), the diffusional and convective fluxes of tracer within the wall can be expressed at any point in the media in a differential form (Patlak et al., 1963; Brace et al., 1978) as:

\[
J_d = -D_w \cdot \frac{dC_t}{dx} \quad (1)
\]

and

\[
J_c = (1 - \sigma) \cdot J_v \cdot C_t \quad (2)
\]

where \( C_t \) and \( dC_t/dx \) are the actual concentrations of tracer and the concentration gradient at that point in the media, \( D_w \) is an effective diffusion coefficient for albumin within the tissue, \( \sigma \) is the reflection coefficient of the wall for albumin. The fluxes are taken to be positive when they occur in the direction of increasing \( x \); i.e., toward the adventitial surface. We have assumed that tracer movement can be considered to be a one-dimensional flux problem.

In the present study, the convective tracer flux, \( J_c \), was opposite in direction to the diffusional flux \( J_d \). When a steady state is attained, the net flux through the wall and at any point within the media
is constant. Under these circumstances, the net tracer flux \( (J_s) \) is given by:

\[
J_s = -D_w \cdot \frac{dC_t}{dx} + (1 - \sigma) \cdot J_v \cdot C_t = \text{Const (3)}
\]

This equation can be nondimensionalized by scaling the length and concentration variables: \( x' = \frac{x}{L} \) and \( C' = \frac{C_t}{C_b} \), where \( x' \) is the fractional distance through the whole medial thickness \( L \), and \( C' \) is the tissue concentration relative to the external bath concentration of the label.

When introduced into Equation 3, this becomes:

\[
J_s' = -\frac{dC'}{dx} + \text{Pe} \cdot C' = \text{Const (4)}
\]

where \( \text{Pe} \) is the Peclet number given by:

\[
\text{Pe} = (1 - \sigma) \cdot \frac{J_v \cdot L}{D_w} \text{ (5)}
\]

and

\[
J_s' = \frac{J_s \cdot L}{C_b \cdot D_w} \text{ (6)}
\]

\( \text{Pe} \) is a measure of the relative contribution of convection and diffusion to the overall tracer flux.

Integration of Equation 4 gives an expression for the concentration profile through the wall:

\[
C' = K_1 + \frac{K_2}{\text{Pe}} \cdot \exp(\text{Pe} \cdot x') \text{ (7)}
\]

where \( K_1 = \frac{J_s'}{\text{Pe}} \) and \( K_2 / \text{Pe} \) is a constant. \( K_1 \) and \( K_2 \) can be defined in terms of boundary conditions. At the luminal surface, the boundary condition equates steady tracer flux \( J_s \) to rates of transport by convection and diffusion through the intima (Truskey et al., 1981). A similar condition applies for the boundary condition at the medial-adventitial interface. These appropriate boundary conditions would necessitate the knowledge of the exact tracer concentrations in the solutions at the intimal and adventitial surfaces, but these are subject to uncertainties, as discussed above. Moreover, these boundary conditions would introduce other unknown parameters to define the different mass transport properties of the intimal and adventitial layers (Truskey et al., 1981). These parameters would be impossible to determine from the data obtained in the present experiments. We have therefore calculated values for \( \text{Pe}, K_1, \) and \( K_2 \) by least-squares fitting of regression lines to the corrected data from Figure 4 using Equation 7. The best-fit parameters were in turn used to calculate theoretical \( C/C_b \) profiles which are superimposed on the experimental data points in Figure 5. The best fit Peclet numbers are given in Table 2. If convection and diffusion contribute equally to transport, then \( \text{Pe} \) would be expected to be approximately one; so it seems that in our experiments the effects of convection are not negligible, particularly in arteries with damaged endothelium, in which transmural fluid flow rates are greater than in intact vessels (Tedgui and Lever, 1984).

Duncan et al. (1965) and Fry (1973) suggested that the effect of transmural pressure on macromolecular uptake was due to stretching, rather than to pressure-driven convection. In their experiments, arteries were pressurized against a supporting screen which may have caused tissue compaction (Harrison and Massaro, 1976). Filtration through vessels pressurized in this way may be diminished by a factor of 10, compared with vessels with normal cylindrical geometry (Yamartino et al., 1974), and any effects of convection on label transport would have been reduced.

The Peclet numbers determined in this study are similar to those determined by Truskey et al. (1981) from a theoretical analysis of the results of in vivo albumin uptake experiments. They estimated Peclet

### Table 2

<table>
<thead>
<tr>
<th>Peclet Numbers, ( K_1 ) and ( K_2 ) (mean ± sd)* for Intact and Deendothelialized Arteries at Transmural Pressures of 70 and 180 mm Hg</th>
<th>Intact endothelium</th>
<th>Damaged endothelium</th>
</tr>
</thead>
<tbody>
<tr>
<td>( 70 \text{ mm Hg} )</td>
<td>( \text{Pe} 4.12 ± 1.10 )</td>
<td>( 5.92 ± 0.94 )</td>
</tr>
<tr>
<td>( K_1 )</td>
<td>( 9.53 ± 6.35 \times 10^{-2} )</td>
<td>( 7.21 ± 5.78 \times 10^{-3} )</td>
</tr>
<tr>
<td>( K_2 )</td>
<td>( 1.87 ± 1.64 \times 10^{-3} )</td>
<td>( 2.08 ± 1.23 \times 10^{-4} )</td>
</tr>
<tr>
<td>( 180 \text{ mm Hg} )</td>
<td>( \text{Pe} 4.65 ± 0.47 )</td>
<td>( 11.25 ± 0.29 )</td>
</tr>
<tr>
<td>( K_1 )</td>
<td>( 9.52 ± 3.72 \times 10^{-3} )</td>
<td>( 3.45 ± 1.84 \times 10^{-3} )</td>
</tr>
<tr>
<td>( K_2 )</td>
<td>( 6.36 ± 5.11 \times 10^{-4} )</td>
<td>( 2.56 ± 3.22 \times 10^{-4} )</td>
</tr>
</tbody>
</table>

* Calculated using Equation 6.
numbers of 3.6 and 13 for intact and deendothelialized vessels, respectively.

It is assumed in the simple theoretical treatment used above that transport properties are uniform across the whole thickness of the media. In fact, our own studies indicate that the distribution volume for albumin in relaxed (Caro et al., 1980b) and air-pressurized arteries (across the walls of which there is assumed to be no convection (Caro et al., 1981)) increases toward the outer surface in a manner dependent on the transmural pressure. In liquid-filled arteries, with the luminal and external surfaces exposed to the same concentration in labeled albumin, the steady tracer distribution is found to be quasi-uniform across the media when the endothelium is removed, whereas a non-uniform distribution is obtained in arteries with an intact endothelium (unpublished data). However, in the latter case, the steady state uptake of labeled albumin may not represent the actual distribution volume for the protein; the distribution volume is an equilibrium parameter which cannot be determined absolutely in a dynamic system. The existence of convective flux, together with a very high resistance to the passage of tracer through the endothelium, would be expected to cause deviation of the steady state concentration values from those which would be determined by the true distribution volume. The greatest deviation may be expected in the inner part of the media, below the endothelium because of the steep concentration gradient across the intima. In deendothelialized arteries, the steady uptake of albumin may give a better indication of the distribution volume because a much less steep concentration gradient occurs at the blood/media interface.

Experiments on the steady state uptake of [14C]-sucrose (a standard tracer for indicating the size of the extracellular space) with the same concentration inside and outside the artery indicate that the extracellular space is fairly uniform across the wall of both intact and deendothelialized vessels (Lever and Tedgui, 1981). Because of the greater diffusion coefficient of sucrose, the convective contribution to its flux is relatively lower than that for albumin. The steady state concentration of sucrose is therefore likely to give a better indication of its distribution volume.

Both steady state sucrose and albumin levels in the wall were greater in deendothelialized than intact vessels. Changes in the available space are likely to affect both the effective diffusion coefficient and the reflection coefficient; an increase in space would be expected to raise the former and decrease the latter. Since these properties are not the same under all experimental conditions, the Peclet number will not truly indicate the importance of convection and of diffusion in a given experimental condition compared to another one. However, it does indicate the magnitude of the convective flux compared to the diffusive flux in each experimental condition. In fact, convection is likely to be even more important in affecting transport across deendothelialized arteries than this analysis would indicate. Although the available space in deendothelialized arteries is probably much greater than in intact arteries, the amount of label which could diffuse into the wall from the outer surface against the convective flux was much less in the former than in the latter.

We wish to thank Professor C.G. Caro for invaluable discussions during this work, and Dr. J. Mikol and Miss M.C. Rouche, Laboratoire d'Anatomie-Pathologie, Hopital Lariboisiere, Paris, for excellent assistance in the histoenzymic studies.

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