Effect of Steric Restriction on the Intracortical Distribution of Microspheres in the Dog Kidney

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SUMMARY The effect on the intracortical distribution of microspheres and radioactivity caused by steric hindrance of the free movement of spheres into afferent arterioles is described by two mathematical models. The results are compared with corresponding experimental data obtained in six kidneys from normotensive dogs. The first model (A) assumes that spheres are located as blood flow, regardless of their size, except for those having diameters greater than that of an afferent arteriole and which do not enter this vessel. The second model (B) includes the Ferry correction. The experimental data show that the percent recovery of spheres with diameters of 20-25 μm was significantly greater in the outer cortex and significantly less in the juxtamedullary cortex than recovery of the smaller spheres, and that the distribution of spheres with diameters of 10 μm to about 17 μm seems uninfluenced by the sphere size. The experimental results obtained in our present study fit best with model A. We found that according to both models steric restriction is a factor of major importance in relation to the intracortical distribution of spheres, and the analysis shows that the blood flow in the inner part of the renal cortex is grossly underestimated by the method of isotope labeled microspheres when diameters of 15 ± 5 μm are used in the dog. Furthermore we found that dilation of the afferent arterioles will change the steric hindrance so that a redistribution of spheres and radioactivity may occur without any redistribution of blood flow. It is suggested that the results interpreted as redistribution of blood flow can be explained as due to altered steric hindrance alone, i.e., as a methodological artifact.

WHEN BLOOD FLOW is measured by isotope-labeled microspheres, it is assumed that the intravascular distributions of blood flow and spheres (or radioactivity) are identical. This assumption probably is valid when the sphere diameter is much smaller than that of the blood vessels, as in measurements of the distribution of blood flow between organs. However, if the diameters of the blood vessels and the microspheres overlap, steric hindrance of the free sphere movement into such vessels may cause an intravascular distribution of spheres (or radioactivity) different from that of the blood flow. This may be the case in measurements of the distribution of blood flow within an organ. The vascular architecture of the renal cortex in the dog, where about 35 afferent arterioles branch off from an interlobular artery running from the juxtamedullary to the outer cortex, offers ideal conditions for exposing this effect.

The range of sphere diameters in the commercially available batches used in most studies extends from 8 to 25 μm. The internal diameter of the afferent arteriole in the isolated kidney has been reported to be 18 and 50 μm in the dog, and 22 μm in the rabbit. On the basis of Poiseuille's equation this diameter has been estimated to about 15 μm in the dog. By mathematical treatment of the frequency distribution of diameters of the injected spheres and of those trapped in the afferent arterioles, the mean diameter of the afferent arterioles in the dog kidney has been estimated to be 16.3 μm (SD = 2.2 μm). There is thus substantial evidence indicating that the diameters of the microspheres used in most research work and the diameters of the afferent arterioles in experimental animals overlap considerably. Consequently, steric hindrance of sphere movement may represent an important error of method when intracortical blood flow distribution is measured by means of isotope-labeled microspheres.

The intent of the present study was to analyze this potential error of method by comparing experimental observations of the cortical distributions of spheres and radioactivity in the dog kidney with two mathematical models for these distributions.

Observations of the Distribution of Spheres in Different Layers of the Renal Cortex in the Dog

The data given in Tables 1 and 2 and in Figure 1 are based on observations in part reported earlier. Six kidneys from three anesthetized, fully grown, normotensive mongrel dogs weighing 13-16 kg, in which microspheres with diameters ranging from 10 to 35 μm were injected through the thoracic aorta, were studied by microscopic analysis of 35-μm-thick sections. The diameters of the spheres and their position in three cortical layers of equal thickness (outer, middle, and juxtamedullary cortex) were recorded. The injected spheres were a mixture of two batches of spheres with average diameters of 15 and 25 μm, labeled with two different isotopes, 144Yb and 85Sr, respectively. The radioactivity of the isotopes in the different cortical layers also was recorded; details of the methods have been described earlier.

The percent of spheres with diameters greater than 20 μm recovered in the juxtamedullary cortex was significantly lower than for spheres of smaller size (Table 1). The percent reduction of spheres recovered in the juxtamedullary cortex seemed to occur when the sphere diameter exceeded 17 μm (Fig. 1). In the outer cortex the percent of spheres greater than 20 μm was significantly greater than for smaller spheres. The percent increase in recovered spheres seemed to occur when the sphere diameter exceeded 20 μm in the outer cortex (Fig. 1). The relative radioactivity per milligram, dry weight, of cortical tissue showed corresponding findings. Related to the radioactivity of the outer cortex (arbitrarily set to 100), the radioactivity of the smaller spheres (15-μm
STERIC RESTRICTION OF SPHERE DISTRIBUTION/Markrid et al.

Table 1  Percent Distribution of Microspheres of Different Sizes among Three Cortical Layers of Equal Thickness

<table>
<thead>
<tr>
<th>Diameter of spheres (μm)</th>
<th>n</th>
<th>Juxtamedullary cortex</th>
<th>Middle cortex</th>
<th>Outer cortex</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: 10-15</td>
<td>366</td>
<td>13.2</td>
<td>35.0</td>
<td>51.8</td>
</tr>
<tr>
<td>B: 15-20</td>
<td>122</td>
<td>12.3</td>
<td>35.4</td>
<td>52.0</td>
</tr>
<tr>
<td>C: 20-25</td>
<td>105</td>
<td>4.6**†</td>
<td>23.6**</td>
<td>72.6**†</td>
</tr>
</tbody>
</table>

Pooled data are from six kidneys of three normotensive dogs. Total number of spheres (n) = 593.

The differences between A and B were not significant (P > 0.05).
* Significant difference between A and C (* = P < 0.05, ** = P < 0.02)
† Significant differences between B and C at the level P < 0.01

As a basis for our mathematical models we have chosen the two principles mentioned. The first model takes into account only the effect of pure geometrical exclusion of spheres with diameters greater than that of the afferent arterioles. The second model uses the same expression for the steric hindrance of the sphere entrance into the afferent arterioles as is found in the Renkin theory of molecular transport through porous membranes (the "ultrafiltration" steric hindrance factor of Ferry).

Mathematical Models of the Sphere Distribution

ASSUMPTIONS

The general problem to be studied is how the geometrical relations between the diameters of injected isotope-labeled microspheres and blood vessels affect (1) the vascular distribution of spheres of different size, and (2) the radioactivity-blood flow ratio in the tissue supplied by arterioles branching off from a larger vessel. The juxtamedullary portion of the interlobular artery in the renal cortex is chosen as an example to illustrate these effects.

The following assumptions have been made: (1) The mixing of microspheres and blood is ideal. (2) The first segment of the main vessel studied (interlobular artery) is presented with the undisturbed diameter-frequency distribution of injected microspheres. (3) The number of microspheres hitting the entrance opening of a side branch vessel is proportional to its blood flow. (4) All the microspheres entering side branches will be trapped in the same cortical layer as the branch. (5) All the branches (afferent arterioles) have the same pressure gradient, and blood flow in them is laminar.

Table 2  Intracortical Distribution of Radioactivity Related to the Outer Cortex

<table>
<thead>
<tr>
<th>Mean diameter of spheres (μm)</th>
<th>Radioactivity (counts/mg dry tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Juxtamedullary cortex</td>
</tr>
<tr>
<td>15</td>
<td>10.2</td>
</tr>
<tr>
<td>25</td>
<td>5.6*</td>
</tr>
</tbody>
</table>

* P < 0.02

The following symbols are used:
∈ = contained within
< > = symbol denoting statistical expectation values
= symbol denoting statistical estimates calculated from experimental data
ρ, r = radius of microsphere, entrance opening of a side branch vessel, respectively.
\( m(\rho), \nu(r) \) = probability density functions (p.d.f.) of \( \rho \)'s and \( r \)'s.

\( \eta, \sigma^2 \) = expectation value (mean) and variance of \( \rho \)

\( \tilde{\eta}, \sigma^2 \) = mean radius divided by standard deviation

\( \xi = \eta / \sigma \) = mean radius divided by \( \eta \)

\( x = \rho / \tilde{\eta} \)

\( z = (r - \xi) / \sigma \)

\( n = \) number of side branch vessels

\( N = \) number of microspheres per unit blood flow or, equivalently, flow concentration of microspheres

\( c = \) radioactivity of microsphere per unit volume

\( q(r) = \) blood flow into a side branch with opening radius \( r \)

\( C, Q, M(\rho) = \) radioactivity, blood flow, and radius frequency distribution of microspheres trapped in the tissue under consideration (a subscript \( T \) denotes their values in the total region supplied from the main stem vessel)

\( R = \left< C / Q \right> = \) radioactivity-blood flow ratio

\( \tilde{a} = \) relative amount of blood flow to the juxtamedullary cortex (JMC)

\( \tilde{M}(\rho), \tilde{M}_r(\rho) = \) experimental frequency histogram for the number of microspheres in the JMC, the total cortex, respectively, \( \tilde{p} \) being a histogram cell midpoint

\( \phi = \) mean tissue blood flow

\( \epsilon = 0, 1 \)

\section*{THEORY}

The number of microspheres with radii \( \epsilon(\rho, \rho + d\rho) \) and with center hitting within an afferent arteriole entrance opening with radius \( \epsilon(r, r + dr) \) is

\[ N \cdot \text{blood flow} \cdot m(\rho) \, d\rho = N_q(r)m(\rho) \, d\rho. \quad (1) \]

The factor \( f(\rho, r) \) is used to express the fraction of Equation 1 that will pass through the entrance opening

Number of spheres entering \( = \) \( N_q(r)f(\rho, r)m(\rho) \, d\rho. \quad (2) \)

Multiplying Equation 2 by the number of entrance openings with radii \( \epsilon(\rho, \rho + d\rho) \) one gets the joint frequency distribution of microspheres with radii \( \epsilon(\rho, \rho + d\rho) \) found in the tissue supplied by afferent arterioles with entrance opening radii \( \epsilon(\rho, \rho + dr) \)

\[ \left[ m \cdot \nu(r) \cdot dr \right] \cdot n \cdot q(r)f(\rho, r)m(\rho) \, d\rho. \quad (3) \]

The frequency distribution of microspheres in the tissue under consideration can be found from Equation 3 by integrating out the \( r \)-dependence (equivalent to summing over all the afferent arterioles)

\[ m(\rho) \, d\rho = nN \cdot m(\rho) \, d\rho \int_0^\infty \nu(r)q(r)f(\rho, r) \, dr. \quad (4) \]

As the radioactivity of a microsphere is proportional to its volume \( = 4\pi r^3/3 \) the expectation value for the tissue radioactivity will be equal to

\[ \left< C \right> = \left< c \cdot \text{volume} \right> = (4\pi c/3) \cdot (\rho^2) = (4\pi c/3) \cdot \int_0^\infty \rho^2 m(\rho) \, d\rho. \quad (5) \]

The expectation value for the tissue blood flow is given by

\[ \left< Q \right> = n \int_0^\infty q(r)\nu(r) \, dr. \quad (6) \]

Because it is assumed that \( q(r) \) is proportional to \( r^4 \) (according to Poiseuille's law) one finally has the following expression for the radioactivity-blood flow ratio

\[ R = \frac{\left< C \right>}{\left< Q \right>} = \frac{4\pi cN}{3} \int_0^\infty \nu(r)q(r)f(\rho, r)m(\rho) \, d\rho \int_0^\infty \nu(r)r^4 \, dr. \quad (7) \]

\section*{Calculated Effect of Particle Retention on the Radioactivity-Blood Flow Ratio}

When the radius of the entrance opening is much larger than that of the microsphere, it is reasonable to expect that

\[ f(\rho, r) = 1. \quad (8) \]

Assuming that Equation 8 is valid for all values of \( \rho \) and \( r \) in the region which contributes significantly to the upper double integral in Equation 7, insertion of Equation 8 in Equations 4 and 7 gives

\[ M(\rho) = nN \cdot m(\rho) \int_0^\infty \nu(r)q(r) \, dr \]

and

\[ R = \frac{4\pi cN}{3} \int_0^\infty m(\rho)r^3 \, dr = R_{\text{max}}. \quad (10) \]

In this case \( M(\rho) \) essentially has the same form as \( m(\rho) \) and is dependent upon the vessel characteristics [i.e., \( \nu(r) \)] only through the tissue blood flow \( \left< Q \right> \). The radioactivity-blood flow ratio, \( R \), is constant and completely independent of the branch vessel characteristics.

However, for purely geometrical reasons one must have

\[ f(\rho, r) = 0 \quad \text{when} \quad \rho > r, \quad (11) \]

i.e., a microsphere cannot enter a side branch vessel with entrance opening radius less than its own radius. It still remains an open question how \( f(\rho, r) \) varies in the interval \( 0 < \rho < r \). As mentioned above, two different hypotheses will be discussed.

Hypothesis A: One might argue that if a microsphere is following the streamlines and its center falls within an entrance opening it finally will be pushed into the vessel. In this situation one might simply put

\[ f(\rho, r) = \begin{cases} 1; & 0 \leq \rho \leq r \\ 0; & \text{otherwise} \end{cases} \quad (12) \]
Hypothesis B: Another theory for steric hindrance to the entrance of spherical particles of radius \( \rho \) into cylindrical pores of radius \( r \) has been put forth in connection with molecular sieving through membranes.\(^*\) Hence one assumes that the correction factor

\[
f(p, r) = \begin{cases} 
(1 - \rho/r)^3 \cdot (2 - (1 - \rho/r)^2), & 0 \leq \rho \leq r \\
0, & \text{otherwise}
\end{cases}
\]  

(13)

describes the actual situation. We think this is too strict a requirement, but until we know how a microsphere actually behaves at an arterial branching point, both alternatives, Equations 12 and 13, shall be evaluated. They both can be combined into a single formula,

\[
f(p, r) = \begin{cases} 
\phi(2 - \rho); & 0 \leq \rho \leq r \\
\phi = (1 - \epsilon \rho/\xi)^2; & \epsilon = 0, 1, \text{ otherwise}
\end{cases}
\]  

(14)

Equation 14 implies that

\[
M(\rho) + m(\rho) \cdot N \cdot \langle Q \rangle
\]  

(15)

and the simple linear relation between radioactivity and blood flow as expressed by Equation 10 has also been lost. Appreciable radiotracer retention in the main stem vessel will occur if the factor \( f(p, r) \) deviates much from 1 in a region of the \( p, r \) plane where \( u(r)^n \) gives its most dominant contribution to the upper double integral in Equation 7. The degree of particle retention will depend upon \( u(r) \) and may therefore be changed by vasomotion of the side branch vessels, even in absence of any flow redistribution.

The Effect of Autoregulatory Vasomotion on \( u(r) \)

The case in which all the side branch vessels change their radii by the same fractional amount or, equally, increase or decrease by the same factor, \( \alpha \), can be expressed by the linear transformation

\[
r' = \alpha r.
\]  

(16)

This would describe the situation when all the vessels exhibited autoregulation due to a changed pressure gradient

\[
\nabla p' = \alpha^{-1} \nabla p,
\]  

(17)

as can easily be shown by application of Poiseuille’s law. The blood flow \( q(r) \) then remains constant and the new p.d.f. of entrance opening radii will be given by

\[
u(r') = u(r) \cdot |dr/dr'| = u(r'/\alpha)/\alpha
\]  

(18)

Nondimensional Analysis and Procedure of Numerical Calculations

The following functions were considered useful to illustrate the effect of particle retention in the main stem vessel:

\[
M(\rho)/M_{\text{max}}(\rho) = \text{normalized number of tissue microspheres as a function of } \rho
\]  

(19)

\[
R/R_{\text{max}} = \text{normalized radioactivity-blood flow ratio.}
\]  

(20)

In fact this means that \( M(\rho) \) and \( R \) are calculated relative to their magnitudes when there is no steric hindrance or geometrical exclusion effect. The advantage of this normalization is that functions approach 1 for parameter values such that \( x \to 0, t \to x \), respectively, i.e., in cases where the vessel mean radius is much larger than that of the microspheres. Moreover \( M(\rho)/M_{\text{max}}(\rho) \) will be completely independent of \( m(\rho) \), the radial distribution of injected microspheres, and is determined only by the side branch vessel characteristics through the form of \( u(r) \).

Assuming that the radial distributions of microspheres and side branch openings are normal as given by Equations A.1 and A.2 in the Appendix, it is possible to write Equations 19 and 20 in a nondimensional form, with parameters \( x, t, k, \) and \( \epsilon \). From these expressions \( M(\rho)/M_{\text{max}}(\rho) \) and \( R/R_{\text{max}} \) were calculated on a NORD-1 digital computer. The z-f-plane was divided into rectangles with side lengths approximately 0.1 and Simpson’s formula was used to evaluate the integrals (a finer division gave no significant improvement in the accuracy of the result). The programs were written in the FORTRAN-4 language.

Calculated Values for \( M(\rho)/M_{\text{max}}(\rho) \) and \( R/R_{\text{max}} \) Related to Experimental Findings

The microscopic examination of the tissue sections showed that \( \tilde{M}(\rho)/\tilde{M}_{\text{av}}(\rho) \)—the relative number of microspheres in the inner third part (JMC) of the dog renal cortex—is a function of the microsphere radius (Fig. 1). Since \( a = (Q)/Q_T \) represents the relative amount of blood flow from the interlobular artery (ILA) to the JMC, \( \tilde{M}(\rho)/\tilde{M}_{\text{av}}(\rho) \) is a statistical estimate for \( M(\rho)/M_{\text{max}}(\rho) \). With pure geometrical exclusion (Equation 12) the latter rapidly approaches 1 when \( \rho \) decreases below \( \xi \), as shown in Figure 2. At small values of \( x \) the relationship \( \tilde{M}(\rho)/\tilde{M}_{\text{av}}(\rho) \) thus should indicate the magnitude of \( a \). The experimental findings show that \( a \) is approximately 0.15 (Fig. 1). When this value for \( a \) is used and the average diameter of the afferent arteriole opening \( 2\xi = 16.3 \mu \text{m (SD = 2.2}\mu\text{m)},

\[
\text{FIGURE 2 Theoretical and experimental curves for the relative recovery of microspheres in the juxtamedullary cortex. Abscissa: microsphere diameter divided by mean afferent arteriolar diameter. Ordinate: ratio between actual recovery of microspheres and injected flow concentration of microspheres. A: the model with pure geometrical exclusion. Equation 12. B: the Ferry correction. Equation 13. The family of curves represents different values of the parameter } k = \text{mean/standard deviation of the afferent arteriolar diameter. Experimental data from six normotensive dog kidneys are plotted in the diagram with the following assumed parameter values: mean afferent arteriolar diameter = 16.3}\mu\text{m, relative amount of blood flow to the juxtamedullary cortex, } a = 0.15. \text{ For further explanation see text.}
\]
which is the calculated value for these kidneys, the experimental findings fit well with the model of pure geometrical exclusion (Fig. 2); an even better fit is produced when the arteriolar diameter is increased to about 18 μm.

To fit the model to the experimental curve when including the Ferry correction, both a and 2\( \xi \) must increase significantly; \( a = 0.40 \) and \( 2\xi = 25 \) μm seem to provide a good approach to the theory, but these figures seem improbably high.

As \( \frac{C}{C_T} \) is the relative amount of measured radioactivity in the JMC, and \( a \) is the relative amount of blood flow, \( \frac{C}{C_T} / a \) should be a statistical estimate for \( R / R_{max} \). In Table 3 and Figure 3 the theoretical ratio \( R / R_{max} \) has been compared to the values of \( C / C_T / a \) obtained in an experiment with two different distributions of microspheres (15 ± 5 μm and 25 ± 5 μm) labeled with different isotopes. The value of \( a \) is used as above. The model based upon purely geometrical exclusion of spheres fits well with the experimental data for the batch of spheres with an average diameter of 15 μm, while the measured radioactivity of the spheres with average diameter of 25 μm is somewhat greater than predicted from the model. The model based upon the Ferry correction deviates markedly from the actually observed values for sphere radioactivity unless the parameter values \( a = 0.40 \) and \( 2\xi = 25 \) μm are used as indicated above.

The model, which only takes purely geometric exclusion into account, thus suggests that the blood flow to the JMC is grossly underestimated when isotope-labeled microspheres with diameters of 15 ± 5 μm or greater are used. As seen from figure 2, the radioactivity-blood flow ratio then will be much smaller than 1 with an afferent arteriolar diameter about 16 μm. This situation is even worse if the "ultrafiltration" steric hindrance factor of Ferry is used.

### The Effect of Vasodilation on \( R / R_{max} \)

As shown in the Appendix, vasodilation due to an autoregulatory response of the afferent arterioles, caused by a lowered blood pressure gradient, will increase \( t \) while \( k \) is unchanged. From Figure 3 it is then seen that \( R / R_{max} \) must also increase. Hence an autoregulatory vasodilation without any change in the blood flow distribution pattern automatically will increase the tissue radioactivity in the first portion supplied by branches from a main stem vessel and consequently reduce the radioactivity in the last part of this vessel. An example of this is given in Figure 3. The p.d.f. of injected microsphere diameters is assumed normal with a mean of 15 μm and standard deviation of 5 μm, and the arrows indicate the change due to a 50% reduction in the pressure gradient over the afferent arteriole, i.e., when \( a = \sqrt{2} \) in Equation 16. It is seen that the model of geometrical exclusion predicts an increase of about 51% of the relative radioactivity in the juxtamedullary cortex when the blood pressure drops, for example, from 140 mm Hg to 70 mm Hg, assuming that the afferent arterioles autoregulate over this pressure range.

### Discussion

The observed differences between the intracortical distribution of the radioactivity of microspheres with different diameters correspond to observations of Katz et al. and have been found constantly in similar experiments in our laboratory. The identical intracortical distributions of spheres with diameters of 18 and 36 μm reported by McNay and Abe are only seemingly in contradiction to this. Recalculation of their data and excluding dogs in which the spheres were injected after reduction of the perfusion pressure, i.e., during vasodilation of the afferent arterioles, shows that in these experiments the relative radioactivity of the greatest spheres also was significantly greater than that of the smaller ones in the outer cortex.

The assumption that all afferent arterioles have the same pressure gradient may be questioned. There are no direct measurements to support this. Theoretical estimations of the hydrostatic pressure drop along the interlobular artery in the dog and direct measurements of the pressure in subcapsular arteries in the rat indicate a substantial pressure drop from the juxtamedullary to the subcapsular part of this vessel. This change in the hydrostatic pressure along the interlobular artery might be compensated for by an increase of the afferent arteriolar diameters. We found, however, that the diameter of the afferent arterioles in the dog was the same in three cortical layers of equal thickness, and Bankir et al. reported it to be even greater in the innermost of four cortical layers. The best estimation of glomerular flow in different cortical layers is given by Källskog et al., who worked with a specially prepared population of isotope-labeled microspheres with diameters of 16.9 ± 2.65 μm, and measured radioactivity of isolated glomeruli. In their studies the glomerular blood flow in the rat kidney was found to be the same in the juxtamedullary as in the superficial glomeruli and slightly greater than in the glomeruli of the middle part of the renal cortex. Bankir et al. worked with a sphere batch with diameter of 15 ± 5 μm and reported a higher glomerular blood flow in glomeruli supplying the vasa recta than in other cortical glomeruli. The question of an identical pressure gradient over the afferent arteriole in all cortical layers remains unanswered. However, as far as the model

### Table 3: Theoretical and Experimental Estimates for the Radioactivity-Blood Flow Ratio in the Juxtamedullary Cortex of the Dog Kidney

<table>
<thead>
<tr>
<th>(2\xi (\mu m))</th>
<th>(k)</th>
<th>(2\xi (\mu m))</th>
<th>(a)</th>
<th>(t)</th>
<th>(a)</th>
<th>(R / R_{max})</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.3</td>
<td>5</td>
<td>15</td>
<td>3</td>
<td>1.09</td>
<td>0.15</td>
<td>0.47</td>
</tr>
<tr>
<td>25</td>
<td>5</td>
<td>0.65</td>
<td>0.05</td>
<td>0.00</td>
<td>0.25 ± 0.13</td>
<td></td>
</tr>
</tbody>
</table>

* For explanation see text.
The finding that reduction of the perfusion pressure below the lower range of autoregulation was without effect on the sphere distribution also is compatible with the model because the afferent arteriolar diameter is uninfluenced by this experiment.

The participation of the afferent arteriole in the different experimental types of induced vasodilation referred to above is not well defined. However, the variations of the intracortical distribution of sphere radioactivity in the experiments mentioned were probably all within an order of magnitude that may be explained by afferent arteriolar dilation and the altered geometrical exclusion effect per se, without the assumption of any redistribution of intracortical blood flow. In experiments with spheres with diameters of 15 ± 5 μm, Abe et al.22 and Stein et al.27 observed a relative increase in the radioactivity of the innermost of four cortical layers of 36% and 45% after perfusion pressure reductions of 41% and 49%, respectively. According to the model of geometrical exclusion these pressure drops will increase the radioactivity in the juxtamedullary cortex by about 39% and 48%, respectively. The observed variations can thus be explained solely by altered geometrical exclusion; it should be underlined, however, that the quantitative aspect of afferent arteriolar participation in the autoregulatory process is disputed.

The well established fact that sympathetic nerve stimulation and infusion of angiotensin II or catecholamines do not alter the cortical distribution of spheres or radioactivity does not invalidate the geometrical exclusion model. Under these experimental conditions the renal blood flow is reduced mainly or solely by the constriction of postglomerular vessels, leaving the afferent arteriolar diameter, and thus the exclusion effect, unaltered.

A discussion of possible effects in addition to the geometrical exclusion will have to be based upon deeper insight into the hydrodynamic phenomena participating in microsphere transport in blood flow. Recent theoretical studies have given the pattern of streamlines when a small vessel branches off from a greater main stem, and indicate that spheres with diameters much smaller than the main stem radius will enter a side branch more easily than larger spheres. Evidence against the presence of more than an insignificant degree of plasma skimming and axial streaming has been presented above. It is difficult to quantify these possible additional effects on sphere distribution. One may tentatively conclude that blood flow and geometrical exclusion seem to be the dominant effects on intravascular distribution of spheres, but, a priori, it seems probable that some unknown additional effect on the intravascular distribution of spheres with diameters less than that of the afferent arterioles may be present. The model based upon the "ultrafiltration" steric hindrance factor of Ferry, which is used in the Renkin theory of molecular sieving through cylindrical pores, seems unable to explain the experimental findings.

In conclusion, the model of geometrical exclusion fits well with the present observations obtained with the microsphere method. The model suggests that the observations interpreted as redistribution of blood flow by this method may be due to a methodological artifact. According to the model of
geometrical exclusion, blood flow measurements by the microsphere method in the renal cortex may be improved by using smaller spheres, preferably between 12 and 14 μm, and with a minimal variation of diameters within the batch. However, the possibility that the distribution of these small spheres also may be influenced by factors other than flow distribution must be kept in mind until the intraorganic flow measurements with the microsphere method can be calibrated against a satisfactory method of reference.

Appendix
DIMENSIONLESS THEORY
Assume that the normal probability density functions

\[ m(\rho) = (2\pi\sigma^2)^{-\frac{1}{2}} \exp\left[-(\rho - \eta)^2/2\sigma^2\right] \]  

(A.1)

and

\[ v(\tau) = (2\pi\sigma^2)^{-\frac{1}{2}} \exp\left[-(\tau - \xi)^2/2\sigma^2\right] \]  

(A.2)

describe the radial distributions of microspheres and entrance openings of afferent arterioles adequately. Substituting Equations A.1 and A.2,

\[ z = (\tau - \xi)/\sigma, \]  

(A.3)

\[ x = \rho/\xi, \]  

(A.4)

and

\[ k = \xi/\alpha \]  

(A.5)

into Equations 4 and 9 in the text, one has

\[ \frac{M(\rho)}{M_{\text{max}}(\rho)} = \frac{\int_k^{\infty} \phi(2 - \phi) \exp\left[-z^2/2\right] (z + k)^4 dz}{\phi(2 - \phi) \exp\left[-z^2/2\right] (z + k)^4 dz} \]  

(A.6)

where

\[ \phi = (1 - ckx/(z + k))^2; \quad \epsilon = 0.1. \]

Equation A.6 is a function of only two parameters, x and k. Substituting further

\[ \xi = (\rho - \eta)/\tau \]  

(A.7)

and

\[ \kappa = \eta/\tau \]  

(A.8)

\[ t = \xi/\eta \]  

(A.9)

and using Equations A.3 and A.5, the expression for R/R_{\text{max}} becomes

\[ \frac{R}{R_{\text{max}}} = \frac{\int_{-\infty}^{\infty} \int_{-\infty}^{\infty} \phi(2 - \phi) \cdot (\xi + \kappa)^4 \cdot (z + k)^4 \exp\left[-(z^2 + z^2)/2\right] dz\, dz}{\phi(2 - \phi) \cdot (\xi + \kappa)^4 \cdot (z + k)^4 \exp\left[-z^2/2\right] dz} \]  

(A.10)

where

\[ \phi = (1 - (ckx/\eta) \cdot (\xi + \kappa)/(z + k))^2 \]

\[ \Xi(\xi) = (k/\xi) \cdot [\xi + \kappa(1 - t)]. \]  

(A.11)

It is readily seen that Equation A.10 is a function of the three dimensionless parameters k, x, and t. The nondimensional expressions in Equations A.6 and A.10 are suitable for numerical calculations.

AUTOREGULATORY VASOMOTION
The transformation in Equation 16 leads to the following expression for the new p.d.f. of afferent arteriole entrance opening radii:

\[ u(t^\prime) = \frac{1}{\alpha} \cdot \exp\left[-(t^\prime - \xi)^2/2\sigma^2\right] \]  

(A.12)

where

\[ \xi^\prime = \alpha \xi \]  

(A.13)

\[ \sigma^\prime = \alpha \sigma. \]  

(A.14)

and using Equations A.3 and A.5, the expression for R/R_{\text{max}} becomes

\[ \frac{R}{R_{\text{max}}} = \frac{\int_{-\infty}^{\infty} \int_{-\infty}^{\infty} \phi(2 - \phi) \cdot (\xi + \kappa)^4 \cdot (z + k)^4 \exp\left[-(z^2 + z^2)/2\right] dz\, dz}{\phi(2 - \phi) \cdot (\xi + \kappa)^4 \cdot (z + k)^4 \exp\left[-z^2/2\right] dz} \]  

(A.10)

where

\[ \phi = (1 - (ckx/\eta) \cdot (\xi + \kappa)/(z + k))^2 \]

\[ \Xi(\xi) = (k/\xi) \cdot [\xi + \kappa(1 - t)]. \]  

(A.11)

References
Errata

In the Brief Review by Arnold Schwartz, "Is the Cell Membrane Na+,K+-ATPase Enzyme System the Pharmacological Receptor for Digitalis?" (Circ. Res. 39: 2-7, July 1976), the second line of the affiliation footnote should read: The Fondren-Brown Cardiovascular Center (instead of Fordham-Brown).

William Withering, cited in the first paragraph of this same article, was never knighted, therefore the title "Sir" before his name is incorrect.
Effect of steric restriction on the intracortical distribution of microspheres in the dog kidney.
L Morkrid, J Ofstad and Y Willassen

Circ Res. 1976;39:608-615
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