Ultrafiltration in Renal Glomerular Capillaries:
Theoretical Effects of Ultrastructure

by

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Abstract

We developed hydrodynamic models for transport of water and macromolecules across the glomerular capillary wall, based on the ultrastructure of its constituent layers. Models were developed for the endothelial fenestrae, basement membrane and epithelial filtration slits with slit diaphragms. The input data included the dimensions of the various structures from previous electron microscopy studies, and the hydraulic permeability recently measured for isolated basement membrane *in vitro*. The model for hindered transport of macromolecules focused on the slit diaphragms and basement membrane.

As a model for flow through the slit diaphragms which connect the epithelial foot processes, we obtained finite element solutions of Stokes' equations for flow perpendicular to a single row of cylinders confined between parallel walls. We computed a dimensionless "additional resistance" (f), defined as the increment in resistance above the Poiseuille flow valve, for $L/W \leq 4$ and $0.1 \leq R/L \leq 0.9$, where L is half the distance between cylinder centers, W is half the distance between walls and R is cylinder radius. Two factors contributed to f : the drag on the cylinders, and the increment shear stresses on the walls of the channel. Of these two factors, the drag on the cylinders tended to be dominant. We also analyzed another representation of the slit diaphragm suggested in the literature, which consists of a certain filament, parallel to the surfaces of the foot precesses and connected to the foot processes by alternating cross-bridges on either side.

We computed velocity and pressure profiles within the endothelial fenestrae and the basement membrane, and calculated the hydraulic permeability of these structures. The results were combined with those for the epithelial slits and the resulting values of the overall hydraulic permeability of the capillary wall (k) agreed very well with an experimental range derived from micropuncture measurements in normal rats. Furthermore, the model provided estimates of the relative contribution of each layer to the total water flow resistance. The hydraulic resistance of the endothelium was predicted to be small, while the basement membrane and epithelial slits were each found to contribute roughly half of the total water flow resistance. When applied to a study of glomerular injury in rats, the model correctly predicted the observed trends in hydraulic permeability.

The hydraulic permeability model was applied also to a study of healthy and nephrotic humans. There was good agreement between the predicted values of hydraulic

permeability (based on measurements of basement membrane thickness and filtration slit frequency) and independent estimates based on hemodynamic measurements and measurements of glomerular filtering surface area. Moreover the model provided an explanation for the fact that reductions of glomerular filtration rate in various human nephropathies tend to be correlated more with reductions in filtration slit frequency than with changes in basement membrane thickness.

To describe the hindered transort of plasma proteins and other macromolecules through the slit diaphragm, we developed an approximate hydrohynamic model for spherical, Brownian particles passing through a row of infinitely long cylinders of macromolecular dimensions. The selectivity of the slit diaphragm was assessed by computing concentration profiles for a wide range of molecular sizes for $Pe \leq 1$, where Pe is a Peclet number based on the cylinder radius. The sieving coefficient for the slit diaphragm was computed as the concentration far downstream (corresponding to Bowman's space) divided by the average concentration at a specified distance upstream from the cylinders (corresponding to the location of the basement membrane). The results of the previous experimental sieving studies using rats could be accounted for approximately by postulating a wide distribution of spacings between the fibers of the slit diaphragm. Calculations made by coupling the results for the slit diaphragm with a model of the glomerular basement membrane suggest that the slit diaphragm is by far the most size-restrictive part of the overall barrier.

In addition we developed a model of glomerular filtration with pulsatile pressures and flows, and used this model as a standard in evaluating the suitability of the usual steady-state formulations. The model included sinusoidal variations in the transcapillary hydraulic pressure and the afferent arteriolar plasma flow rate over each cardiac cycle. The analysis suggested that the previously ignored time derivatives in the luminal mass balances are not negligible, and that the oscillations in pressure are sufficieint to cause filtration reversal at the more efferent locations in a capillary. However the time-averaged values of glomerular filtration rate and sieving coefficients for macromolecules were not significantly different from those for a steady-state formulation. This supports the validity of the steady-state assumption used in previous models of glomerular filtration as well as in the hydrodynamic models described in this thesis.

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