PVP-Sieving Curves as an Estimate of Glomerular Hemodynamics in HgCl$_2$
Acute Renal Failure in the Dog

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In the present study, the pathophysiologic role of glomerular hemodynamic factors in the early phase of HgCl$_2$-induced acute renal failure is evaluated in the dog. This model of moderate ARF is characterized by a parallel fall in glomerular filtration rate (ΔGFR, -43%) and renal blood flow (ΔRBF, -38%) within the first three hours after HgCl$_2$ administration. Glomerular hemodynamics were studied by analysis of PVP-sieving curves. There was a significant shift of these curves upward and to the right during the 3 hours that followed the injection of HgCl$_2$. From this analysis, no arguments for tubular back-leak could be found. Mathematical analysis of the curves revealed a fall in effective filtration pressure (EFP) in presence of an unchanged glomerular ultrafiltration coefficient (Kf) (ΔEFP, -40±4% ; p<0.01; ΔKf, +5± 1%; p>0.05 vs. control). No major changes occurred in glomerular colloid osmotic pressure. Subsequently, the early fall of GFR in this toxic model of acute renal failure was essentially attributed to a decrease of effective filtration pressure due to either tubular obstruction and/or mainly to renal hemodynamic changes.

Renal vasoconstriction occurs during the early phase of acute renal failure (ARF). Nevertheless, the pathophysiologic role of renal hemodynamic changes remains unclear. The absence of any beneficial effect of maintaining a normal renal blood flow (RBF) on glomerular filtration (GFR) in many toxic models makes doubtful vasoconstriction as a major role in the pathophysiology of early ARF.

If a glomerular hemodynamic factor was involved in the initiation of ARF, then the fall in GFR should be mediated by either a decrease in intraglomerular effective filtration pressure (EFP) and/or by a decrease in glomerular ultrafiltration coefficient (Kf). Direct estimations of both glomerular parameters in experimental ARF are scarce, and the reported results are often inconsistent.

In human forms of ARF, evaluation of glomerular dynamics is necessarily indirect, and the only available technique that has been applied is the analysis of macromolecular glomerular sieving curves. Myers and coworkers, using this method in forms of postoperative ischemic ARF, were able to observe remarkable shifts of the macromolecular sieving curves compatible with either tubular back-leak in severe ARF or a fall in filtration pressure in milder forms. Similar data on experimental ARF are as yet unavailable.

Therefore, in the present study of early phase toxic ARF, macromolecular glomerular sieving curves were obtained to determine whether a change in EFP or Kf accompanied the fall in GFR after HgCl$_2$ in the experimental dog model. The results indicate that, at least in the early phase, this model is characterized by an important fall of EFP without substantial changes in glomerular permeability.

Materials and Methods

The studies were performed in 15 mongrel dogs. After anesthesia with pentobarbital (30 mg/kg i.v.), surgical preparation and clearance studies were performed as previously reported.

Clearance Studies

After 3 control clearance collections had been obtained, HgCl$_2$ (3 mg/kg bolus i.v.) was administered. Experimental clearances were collected 1, 2, and 3 hours after the HgCl$_2$ administration. Exogenous creatinine and inulin clearances were obtained as an estimation of GFR. RBF was calculated from paraaminohippurate (PAH) clearances and renal venous blood PAH extractions obtained via a small catheter, introduced into the renal vein through the gonadal vein. Filtration fraction (FF), fractional sodium excretion (FENa), and urinary osmolar excretion (UV) were determined according to standard methods.

To perform the clearance determinations, 2 g inulin, 375 mg creatinine, and 150 mg PAH were injected intravenously as a bolus over a 15 minute period. The markers were then further infused continuously at a rate of 40, 7.5, and 3 mg/min, respectively. Blood colle-
tions for clearance studies were obtained at least 1 hour after the initial bolus injection. No major changes were seen in the plasma concentrations of these three substances during the 3-hour study period.

**PVP-Sieving Studies**

Renal glomerular dynamics were studied by means of PVP-sieving curves. Fractional clearances of PVP molecules of different size (2–4 nm) were determined during the control period before the mercury administration and 3 hours after HgCl₂. Pluridisperse solutions of radioactive iodinated polyvinylpyrrolidone (¹²⁵I PVP) i.v. were administered as described previously.¹⁴ Urine and plasma samples were collected to be chromatographed, allowing the separation of samples of different molecular sizes and the calculation of their fractional macromolecular clearances. Chromatographies were performed on Sephadex G 200 columns, 46 cm long and with a 5.3-cm² basic surface area. The Sephadex G 200 gel consisted of particles with a diameter of 40–120 μ, a volume of 30–40 ml/g dry weight and was dissolved in isotonic saline.

Identification of the Einstein-Stokes radii (aₜ) of the different chromatographed fractions was based on the calculation of the partition coefficient Kₚ according to the formula:

\[
K_p = \frac{V_v - V_e}{V_v - V_o} \tag{1}
\]

where \(V_v\) is the elution volume of the given fraction, \(V_e\) is the void volume of the chromatography column (the peak elution volume of dextran blue), and \(V_o\) is the total volume (the peak elution volume of KCl).

The relation between the aₜ and Kₚ was determined for each column before the start of the experiments. This calibration procedure was performed with 6 homogeneous neutral dextran fractions with known Einstein-Stokes radii, resulting in a linear regression equation:

\[
\log a_t = a(1 - K_p) + b \tag{2}
\]

Factors a and b are specific for each column and approximate 0.75 and 1.10, respectively.

Based on these data and conforming with the literature, fractional PVP clearances or sieving coefficients were calculated for each of the Einstein-Stokes radii of the studied molecules (ranging from 2–4 nm), and these figures were related to each other in the sieving curves.

**Evolution of Glomerular Dynamics (EFP and Kf)**

The magnitudes of EFP and glomerular permeability (Kf), which determine filtration, influence the shape of the sieving curve. The relative evolution of these values can be calculated based on the sieving data using a computer program as first described by Dubois et al.¹⁵ This approach also allows for the estimation of the relative evolution of the glomerular pore size (R) and the available filtration surface area per unit of length (Ap/Δx). The latter parameters are the main factors that influence Kf. These derived values for estimating glomerular dynamics and sieving coefficients have been validated in previous work by one of the authors.¹⁶

**Relation of Experimental and Control Sieving Coefficients (Φₑ/Φₑ₉ₒ₉)**

These studies were undertaken within the context of Myers et al.¹⁶ whose arguments in favor of tubular back-leak in human postsurgical ischemic ARF were based on the evolution of macromolecular sieving curves. Their arguments were based on the steady increase in the relation \(Φₑ/Φₑ₉ₒ₉\) with increasing macromolecular diameters up to a plateau value for the largest molecules studied. This phenomenon is explained by a relative underestimation of the inulin clearance as a consequence of a more important back-leak of this marker, compared with the macromolecules.

To compare our results with those of Myers et al.,¹⁶ the same relation \(Φₑ/Φₑ₉ₒ₉\) was calculated. Calculations were only performed for \(Φₑ₉ₒ₉\) values of 0.10 or more. Indeed, for smaller \(Φ\) values, minor differences in the range of 0.01 or even less may induce major differences in the final results (changes of 10% or more).

**Plasma Colloid Osmotic Pressures**

Plasma colloid osmotic pressures were calculated from plasma protein concentrations, C, as first described by Navar et al.¹⁷ according to the formula:

\[
\pi = (a \times C) / 1 - (b \times C) \tag{3}
\]

In Navar’s formulation, a is 2.05 and b is 0.035. This relation is based on refractometric determinations of plasma protein concentrations, whereas in the present study the biuret method was used. This method is known to result in protein concentrations that are slightly lower compared with the results obtained with refractometry.¹⁷ Consequently, the relation between \(C\) and of (determined by the biuret method) was calculated in a preliminary study on 56 plasma samples with protein concentrations ranging from 4–10.5 g/dl. For this purpose, samples of animals in dehydrated, rehydrated, or overhydrated conditions were studied. Some of these samples were further diluted or concentrated to obtain more extreme values of protein concentrations. Colloid osmotic pressure was measured by means of the BMT 921 Onkometer (BMT Messtechnik GMBH, Berlin, FRG).

The relation between plasma colloid osmotic pressure and plasma protein concentrations resulted in the relation (Figure 1):

\[
\pi = (2.37 \times C) / 1 - (0.038 \times C) \tag{4}
\]

Glomerular colloid osmotic pressure was calculated in 2 different ways. First, as the average of preglomerular and postglomerular colloid osmotic pressure (\(\pi_x\) and \(\pi_y\)). Both values were calculated from the afferent and efferent protein concentrations (\(C_A\) and \(C_E\)). \(C_x\) is the peripheral arterial blood protein concentration, and \(C_e\) is calculated from \(C_A\) and the filtration fraction:

\[
C_e = C_x/(1 - FF) \tag{5}
\]
"If
Q. m 3
5 2
•M'
K.
2.37 X C
l-(0.038 X C)
0 5 10 15 20 25 30 35 40
Colloid osmotic pressure \(\pi\) (mm Hg)
FIGURE 1. Relation between colloid osmotic pressure \(\pi\) and plasmatic protein concentration \(C\). Results were determined from 56 plasma samples with a concentration of 4–10.5 g/dl. The relation between \(\pi\) and \(C\) was calculated to be:
\[\pi = \frac{2.37 \times C}{1 - (0.038 \times C)}\]

Second, the glomerular colloid osmotic pressure also was calculated as the integrated mean value, as derived from the model of Dubois et al.\(^5\)

Statistical Evaluation
Results are given as mean ± SEM. Comparison of the experimental values with the control values was obtained by Wilcoxon’s test for paired observations.

Results
Clearance Studies
The results of the clearance studies are illustrated in Table 1. There was a progressive fall in GFR and RBF and a rise in urinary volume, FE\(_{Na}\), and UV\(_{Osm}\). Both mean arterial pressure (MAP) and FF, after an initial rise during the first hour after HgCl\(_2\), normalized and approached the control values during the third hour after HgCl\(_2\). There were no significant changes in extraction of para-aminohippurate (E\(_{PAH}\)).

The relation of creatinine and inulin clearances (C\(_{cre}\)/C\(_{iri}\)) was calculated; the values remained unaltered over the entire experiment: 0.99±0.04, 0.97±0.03, 0.96±0.04, and 0.99±0.04 for the control period and 1, 2, and 3 hours after HgCl\(_2\), respectively (\(p>0.05\) vs. control).

Evolution of PVP-Sieving Curves
The evolution of the macromolecular sieving curves (range 2–4 nm) is illustrated in Figure 2. There is a shift of the curve upwards and to the right 3 hours after the HgCl\(_2\)-administration. It should be noted that no \(\Phi\) values greater than 1.0 were observed after the mercury administration. These functional clearances were calculated in relation to inulin clearances. If these same calculations were repeated in relation to the clearances of the much smaller creatinine molecule, the same results were obtained.

Evolution of Glomerular Dynamics
Using a computerized mathematical approach as described by Dubois et al., an absolute mean control value of EFP of 4.2±0.5 mm Hg was obtained (Table 2). A Kf value of 14.3±2.0 ml/min/mm Hg per 100 g kidney weight was calculated. Assuming that each gram of kidney tissue contains 13,000 glomeruli, a control Kf value per nephron of 11.0±1.5 nl/min/mm Hg was obtained.

The percentage change of parameters that determine glomerular filtration, 3 hours after HgCl\(_2\) vs. control,

Table 1. Results of the Clearance Studies (n = 15)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>1 hr after HgCl(_2)</th>
<th>2 hrs after HgCl(_2)</th>
<th>3 hrs after HgCl(_2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR/100g KW</td>
<td>75.5±3.5</td>
<td>70.5±3.5</td>
<td>50.4±3.4</td>
<td>43.4±2.8</td>
</tr>
<tr>
<td>RBF/100g KW</td>
<td>552±33</td>
<td>445±33</td>
<td>359±42</td>
<td>344±27</td>
</tr>
<tr>
<td>V/100g KW</td>
<td>0.34±0.11</td>
<td>1.64±1.55</td>
<td>2.63±0.42</td>
<td>2.49±0.25</td>
</tr>
<tr>
<td>FE(_{Na})</td>
<td>0.45±0.18</td>
<td>3.77±1.17</td>
<td>8.61±1.71</td>
<td>9.32±1.39</td>
</tr>
<tr>
<td>UV(_{Osm})</td>
<td>364±40</td>
<td>967±268</td>
<td>987±240</td>
<td>880±240</td>
</tr>
<tr>
<td>E(_{PAH})</td>
<td>80±2</td>
<td>82±2</td>
<td>83±3</td>
<td>81±2</td>
</tr>
<tr>
<td>FF</td>
<td>29±3</td>
<td>37±3</td>
<td>34±3</td>
<td>28±2</td>
</tr>
<tr>
<td>MAP</td>
<td>128±4</td>
<td>140±5</td>
<td>137±5</td>
<td>130±5</td>
</tr>
</tbody>
</table>

GFR, glomerular filtration rate; KW, kidney weight; RBF, renal blood flow; V, urinary volume; FE\(_{Na}\), fractional sodium excretion; UV\(_{Osm}\), urinary osmolar excretion; E\(_{PAH}\), extraction of para-aminobiphenurate; FF, filtration fraction; MAP, mean arterial blood pressure.

*p < 0.05 vs. control; †p < 0.01 vs. control.
Table 2. Filtration Determinants 3 Hours After HgCl₂

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>HgCl₂</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kf (ml/min/mm Hg)</td>
<td>14.3±2.0</td>
<td>14.9±1.5</td>
<td>+5±1%</td>
</tr>
<tr>
<td>EFP (mm Hg)</td>
<td>4.2±0.5</td>
<td>2.5±0.3*</td>
<td>-40±4%</td>
</tr>
<tr>
<td>R (nm)</td>
<td>5.0±0.1</td>
<td>5.1±0.1</td>
<td>+2±1%</td>
</tr>
<tr>
<td>Ap/Δx (cm×10⁶)</td>
<td>0.4±0.1</td>
<td>0.4±0.1</td>
<td>—</td>
</tr>
</tbody>
</table>

*p<0.01 vs. control.

are also summarized in Table 2. A relatively constant value of Kf and of its constituents R and Ap/Δx was observed three hours after HgCl₂. EFP fell by 40% during the third hour after HgCl₂ (p<0.01).

Evolution of the Relation Oₗ/Ω conro

The evolution of these values is illustrated in Figure 3. In contrast with the findings of Myers et al.,¹⁰ which were obtained in established human postischemic ARF, the relation Oₗ/Ω conro in our experiments, does not reach a plateau for the larger macromolecules at 3 hours after HgCl₂. The Oₗ/Ω conro value for a molecular radius of 3.8 nm was significantly lower than the maximum value obtained at 3.5 nm radius (p<0.05).

Glomerular Colloid Osmotic Pressure

Based on formula 4, no significant changes in afferent, efferent, and mean glomerular colloid osmotic pressures (πo) were calculated within the first 3 hours after HgCl₂; the control value of πo was 21.64±0.48 mm Hg, whereas a value of 22.52±0.53 mm Hg was obtained 3 hours after HgCl₂ (p>0.05). Calculation of πo by the integrated mean method revealed a control value of 21.68±0.35 mm Hg and an experimental value of 22.65±0.61 mm Hg. The values calculated by the two methods were not different.

Discussion

In this study, the evolution of the sieving curves of neutral PVP and of glomerular hemodynamics is evaluated in the early hours of HgCl₂-induced ARF. The pathophysiology of ARF after HgCl₂ has been the subject of extensive study, and this model can be considered as a valuable experimental model of toxic ARF and a clinically relevant one since heavy metals remain an important cause of nephrotoxicity.¹⁸ The in vivo evolution of both glomerular permeability and intraglomerular pressure early after HgCl₂ has not yet been studied.

In previous studies from this laboratory, it was found that HgCl₂ (3 mg/kg i.v.) was followed by a rapid but moderate deterioration of both RBF and GFR.⁴⁻⁹ This model is, therefore, particularly appropriate for the evaluation of glomerular hemodynamics in the initiation phase of mild ARF. Many other studies dealing with this problem were concentrated on the late phase and on more pronounced forms of ARF.⁴⁻⁹

Sieving curves of macromolecules have been frequently used in the study of the physiology of glomerular filtration,²¹⁻²² of the mechanisms of proteinuria,¹₂⁻²₃ and of the pathophysiology of human postischemic ARF.¹₀⁻¹₁,¹₃ In view of the latter studies, it was interesting whether this method should lead to comparable results in the more controlled setting of a well-defined acute toxic lesion. From the shifts in the sieving curves, the role of the different determinants in the filtration process can be approximated.

As can be noted from Figure 2, the sieving curves show a significant shift to the right during the 3 hours that followed the administration of HgCl₂. One possible explanation for such a shift would be the presence of tubular back-leak of smaller molecules, in the range of inulin and/or creatinine, traditionally used as filtration markers. When renal function is normal, all inulin and PVP molecules are supposedly cleared by the glomerulus and appear in the final urine. For the kidney in ARF, the presence of back-leak is essentially related to inulin and small PVP molecules, but its presence may be diminished for larger PVP molecules and may even be absent for the largest PVP molecules (>3.2 nm). This back-leak results in an underestimation of true glomerular inulin clearances and an overestimation of fractional PVP clearances, resulting in a shift to the right of the sieving curve. Although similar shifts can occur under other circumstances, it is typical that a plateau value is reached for Oₗ/Ω conro relative to the degree of back-leak. For example, a plateau value of Oₗ/Ω conro of 2.0 suggests a decrease by 50% of apparent GFR due to back-leak. In this case, a Oₗ/Ω conro value exceeding unity should be expected for the smaller molecules (range 2–3 nm). Furthermore, this should be accompanied by a rise of the fractional macromolecular clearances of the larger molecules (>3.0 nm) in proportion to the degree of back-leak. This phenomenon has been described on several occasions by Myers et al in the case of postsurgical, severe ischemic ARF in man.¹₀,¹₂ In contrast, the same authors were not able to demonstrate these findings in a milder form of human ischemic ARF.¹₃

In the absence of a plateau for Oₗ/Ω conro, an eventual shift to the right of the sieving curve should be attributed to another pathophysiologic event, such as a
decrease in effective filtration pressure. In the present study, no plateau in \( \Phi_{out}/\Phi_{in} \) for \( \Phi_{out} \) values exceeding unity for smaller molecules were observed. Consequently, these data give little support in favor of eventual tubular back-leak.

Furthermore, the relation \( C_{ina}/C_{io} \) remained unchanged throughout the entire experiment, and fractional PVP clearances related to \( C_{ina} \) had the same configuration as those calculated from inulin clearances, excluding a selective back-leak of molecules in the smaller molecular range.

Finally, the renal venous \( E_{PAH} \) remained unchanged during the 3 hours after \( HgCl_2 \). In the presence of back-leak, a decrease of this extraction in proportion with tubular dysfunction may be supposed.

The absence of back-leak is in disagreement with two previous functional and morphologic studies in \( HgCl_2 \) ARF in the rat, but it is in agreement with three more recent studies. All these previous data, however, were obtained at least 24 hours after the injection of \( HgCl_2 \); therefore, a comparison with the present data is not possible. The present data do not, then, exclude back-leak as an additional pathophysiologic factor in the later maintenance phase of this model.

A second reason for a shift to the right in the sieving curve, is a rise in \( Kf \) and/or a decrease of EFP. A rise of \( Kf \) is highly improbable, especially in the presence of a 40% fall in GFR. A fall in EFP may cause also the decrease in GFR and shift of the sieving curve to the right after \( HgCl_2 \). This supposition is confirmed by the mathematical analysis of the relative changes in \( Kf \) and EFP.

As can be noted from Table 2, focus is on the relative changes beside the absolute parameters derived from the mathematical analysis of the sieving curves; we have concentrated on these for two reasons. First, as summarized in Table 3, some differences already exist in the shape of the control sieving curves, not only between different species but also within the same species. For example, the sieving coefficients for a molecular radius of 3.2 nm in man range from 0.44–0.55, in rats from 0.16–0.42, and in dogs from 0.22–0.36 (Gassee et al, Vanrenterghem et al, and present data). Although seemingly small, this variability may result in substantial differences in the calculated glomerular dynamic parameters, making it difficult, in our opinion, to translate these sieving data into exact numbers of membrane permeability and transmembrane pressure. Second, at the present state, it is difficult to define an exact absolute value for \( Kf \).

As noted in Table 4, highly divergent results for \( Kf \) and consequently for EFP have been obtained. Although these discrepancies in part can be explained by different techniques used in different conditions, it is fair to state that an exact value for \( Kf \) and, consequently, for EFP cannot yet be given. Furthermore, data derived from micropuncture can only be applied to the surface glomeruli, while macromolecular sieving-curve data integrate the results of the total glomerular population.

The present findings of an unaltered \( Kf \) and a fall of EFP are in agreement with several other studies like this one, in which ARF is related to moderate functional disturbances. First, in an in vitro study by Cachia et al on isolated glomeruli in the rat revealed unaltered \( Kf \) values 24 hours after the administration of \( HgCl_2 \), in a dosage comparable to the one used in the present study (4 mg/kg); however, a higher dose of \( HgCl_2 \) (10 mg/kg)
caused a significant fall in Kf with 39%. These data underscore the importance of the administered dose on the final lesion determining the filtration fall in ARF. Second, Eknayan et al. performed a morphometric evaluation in the rat of glomerular basement-membrane pore size and surface area after HgCl₂, and they found no significant changes in these two parameters, suggesting, albeit indirectly, that Kf itself remains constant in this model. In addition, Daugherty et al. provided arguments that a fall of Kf was not obligatory to provoke a decrease of single nephron GFR after 3 hours of partial ischemia in the rat with a 39% concomitant decrease of glomerular plasma flow. Finally, Myers et al., making use of the same macromolecular sieving method as the one used in the present study in human postsurgical mild renal ischemia, obtained almost identical results as the present study in showing a fall in EFP. All these data, therefore, support the notion that a fall of EFP without alteration of Kf accounts at least in part for the early reduction of GFR in these milder forms of ARF.

On the other hand, there are several other studies, most of them based on micropuncture data, that point to a fall of Kf as a major pathogenetic mechanism in ARF. Blantz described a fall of Kf in combination with a rise in EFP 2 hours after uranyl nitrate in the rat. Similarly, in the same species, Baylis et al. and Schor et al. found a fall of Kf 10 days after high doses of gentamicin. Williams et al. described a decrease of Kf 48 hours after 60 minutes of renal ischemia in the dog.

The discrepancy between these studies and our results might be due to several factors. Most of these micropuncture studies were performed either in a later stage of ARF when RBF had returned to its control value or in a model where renal hemodynamics remained unaltered. Furthermore, these micropuncture studies are based on data exclusively obtained in superficial subcapsular nephrons. In the postischemic rat model of ARF, Mason et al. demonstrated that SNGFR measured in these very superficial nephrons might not be representative for what is occurring in somewhat deeper nephrons. We tried, therefore, to estimate both glomerular permeability and filtration pressure by a method evaluating the whole nephron population.

The decrease in EFP can be attributed to several mechanisms: a rise in glomerular colloid osmotic pressure or in proximal tubular hydrostatic pressure, or a decrease of glomerular capillary hydrostatic pressure, or a combination of all these factors. A rise in glomerular colloid osmotic pressure was not observed 3 hours after HgCl₂. Based on the sieving curve data only, it is impossible to discern between the two remaining mechanisms. One mechanism that should be considered in this discussion is the rise in proximal tubular pressure due to a major decrease in proximal tubule reabsorption of water and electrolytes, even in the absence of renal tubular obstruction. Consistent with this possibility is the massive natriuresis that was observed 3 hours after HgCl₂ (Table 1).

On the other hand, most micropuncture and/or morphologic studies disfavor a major role of tubular obstruction in the early phase of HgCl₂-induced acute renal failure. In addition, in previous studies of our group in the HgCl₂ model, no arguments for tubular obstruction could be found. It is, therefore, suggested that hemodynamic factors are at least partly responsible for the fall in effective filtration pressure.

In conclusion, the fall in GFR and RBF 3 hours after HgCl₂, was associated with a shift to the right of the macromolecular sieving curves. A host of data excluded tubular back-leak as a major pathophysiologic mechanism for the decrease in filtration and the accompanying shift of the sieving coefficients. A fall of glomerular permeability was also highly improbable. Subsequently, the changes in this model of mild ARF could be attributed to a fall in effective filtration pressure either due to tubular obstruction or to hemodynamic changes. The present data do not allow for the discrimination between these two mechanisms. Based on previous studies of this model, hemodynamic factors are at least in part responsible for this fall in effective filtration pressure.

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