A Mathematical Analysis of the Myogenic Hypothesis with Special Reference to Autoregulation of Renal Blood Flow

Alf H. Øien and Knut Aukland
From the Department of Applied Mathematics and Department of Physiology, University of Bergen, Bergen, Norway

SUMMARY. To test the hypothesis that autoregulation of renal blood flow could result from myogenic regulation of arterial/arteriolar wall tension, we have explored a model based on the assumptions that (1) each preglomerular vessel segment reacts to a change in transmural pressure by altering its internal radius until the initial change in wall tension is reduced by a gain factor, (2) postglomerular structural resistance remains unchanged, (3) extravascular tissue pressure equals intrarenal venous pressure, and (4) the renal vascular system can be represented by one unbranched tube. General equations were obtained for flow and segmental radii and pressure as functions of aortic pressure. With a gain factor of 1 and a glomerular capillary pressure of 50% of aortic pressure under control conditions, the model predictions agree well with experimental data in dogs. Increasing aortic pressure from about 60% of control level causes only slight increase of blood flow. A rise in tissue pressure up to 40% of aortic pressure causes only moderate reduction. Changes in vessel radii begin in proximal vessel segments and spread distally toward glomerulus at increasing changes in aortic and tissue pressures from their control levels. Glomerular capillary pressure is autoregulated in proportion to blood flow. The degree of autoregulation is only moderately dependent on the gain factor: A moderate impairment caused by reducing the gain factor from 1 to 0.7 may be compensated by locating the myogenically responsive wall layer a distance 0.2 times the internal radius from the vessel lumen. "Superautoregulation," i.e., a rise in flow at reduced aortic pressure, is not possible. An upper limit of autoregulation is obtained only with the additional assumption of a fall in contractile force at extreme shortening of the muscle fibers. No definitive biological proof has yet been provided for a segmental wall tension-regulating mechanism in the preglomerular vessels, and obviously its existence cannot be proved by a mathematical model. However, if such a mechanism does exist, it can explain most of the renal resistance changes at varying arterial and intrarenal pressures, as well as the observed autoregulation of terminal interlobular arterial pressure. (Circ Res 52: 241–252, 1983)

THE kidney, like several other organs, shows autoregulation, defined as "an intrinsic tendency of an organ to maintain constant blood flow despite changes in arterial perfusion pressure" (Johnson 1964). Thus, renal blood flow (RBF) will remain unchanged when the arterial pressure is varied in the range of 60–80 to 200–300 mm Hg (Shipley and Study, 1951; Thurau and Kramer, 1959). It is generally agreed that this is accomplished mainly through regulation of the tone of the smooth muscle of the preglomerular vessels, controlling the radius and, thereby, the structural resistance of these vessels. However, the initiation and control of this response remain unclear. The tubuloglomerular feedback hypothesis supposes that the preglomerular resistance is regulated through a signal dependent on flow rate in the distal tubule, which in turn depends on glomerular capillary pressure and RBF. In spite of the attractive negative feedback in this model, and the well-documented existence of a flow-dependent signal from the distal tubule, many investigators still believe that this mechanism is inadequate to account for the autoregulation (Stein, 1976; Hollenberg, 1979; Wright and Briggs, 1979; Kiil, 1981). An alternative is a direct vascular response to luminal pressure, as first proposed by Bayliss in 1902: "The muscular coat of the arteries reacts to a stretching force by contraction" and "to a diminution of tension by relaxation, shown of course, only when in a state of tone." This property, later referred to as the "Bayliss mechanism," the "myogenic response," or the "myogenic mechanism," has the apparent drawback that flow is not the con-
trolled variable and gives no feedback to the preglomerular vessels. Accordingly, it has been difficult to envisage a coupling between intraluminal pressure and muscle contraction that would serve to maintain constant flow.

In order to prevent flow increase at a rise of perfusion pressure, the preglomerular vessels have to respond with a reduction of radius, i.e., by a shortening of the wall circumference. As recently discussed by Johnson (1980), this cannot be achieved as a steady state response with a sensor in parallel with the contractile element, leading to the postulate of a series-coupled sensor. In that case, the contraction itself will not reduce the stimulus of a pressure rise, but the resulting reduction of vessel radius will reduce the wall tension according to the Laplace relationship: 

\[ T = P \cdot r \]

where \( T \) is the total circumferential wall tension per unit vessel length, \( P \) is the transmural pressure, and \( r \) is the vessel radius. Accordingly, it has been proposed that the "aim" or setpoint of the myogenic response would be to maintain constant wall tension (Thurau, 1964). It does not follow, however, that flow is maintained, and several investigators have in fact rejected the hypothesis, claiming that it would lead to reduction of flow at increased pressure (Thurau, 1967; Navar, 1978). This problem could be remedied by a suitable low feedback gain (Johnson and Intaglietta, 1976). However, as pointed out by Kiil (1975) and Aukland (1976), the objection rests on the erroneous assumption that all segments of the resistance vessels are exposed to the full change of arterial pressure. According to this concept, a rise in arterial pressure leads to contraction and narrowing of the proximal myogenic vessels, increased resistance, and pressure fall through this segment, and thereby largely prevents the stimulus for contraction from reaching the more distal arteries arterioles.

A much more satisfactory solution was recently reached by Johnson (1980), who considered the resistance vessels as a series-coupled arrangement of independent effectors, each unit responding to changes in its own wall tension. According to this concept, a rise in arterial pressure leads to contraction and narrowing of the proximal myogenic vessels, increased resistance, and pressure fall through this segment, and thereby largely prevents the stimulus for contraction from reaching the more distal arteries arterioles.

The aim of the present study is to make a quantitative evaluation of this "descending myogenic auto-regulation" with special reference to the renal circulation, by testing in a model with fully defined parameters: (1) the influence of varying the feedback gain, (2) the effect of assuming the sensor to be located at some distance from the luminal surface of the vessel, and (3) the effect of varying the autoregulated, preglomerular fraction of the total renal resistance. For each of these cases, and for some combined parameter changes, we obtained the relationship of flow to perfusion pressure, as well as the pressure and radius profiles along the myogenically active vessel segments.

Finally, we compare the model predictions to experimental data, in order to evaluate whether the postulated segmental wall tension regulation is a possible explanation of autoregulation of renal blood flow.

**General Description of the Model**

The renal arterial blood vessels divide in numerous parallel channels, ultimately into afferent arterioles, each supplying one glomerulus. To handle this complex system, we make the assumption that blood flow to each of these parallel channels is regulated proportionately at changes in arterial pressure (see Discussion). This reduces the model to one of series resistances, and we may now represent the renal blood vessels by one unbranched tube of uniform inner control radius (\( r \)), where the lengths of the vessel segments are scaled according to their resistances. This implies a linear pressure drop along the length axis under control conditions. It also implies that the relatively long intrarenal arteries (interlobar and arcuate arteries) are represented by short lengths in the tube model because of their low resistance, whereas the afferent and efferent arterioles are represented by greater lengths. It also follows that a given point at the tube may represent both afferent arterioles of deep glomeruli and interlobular arteries, as indicated in Figure 1.

To define the model further, we make the following assumptions:

1. For all segments of the tube, we assume that the blood flow is determined by the Hagen-Poiseuille relationship.
2. We assume that the external pressure (\( p_e = \) "tissue pressure") exerted on the intrarenal vessels is equal to the intrarenal venous pressure (\( p_v \)), and independent of aortic pressure (\( p_a \)). The pressure drop from the intrarenal veins to the renal vein is thus assumed to be wholly determined by the tissue pressure ("vascular waterfall"). Accordingly, the perfusion pressure is equal to arterial pressure minus tissue pressure. The preglomerular resistance fraction under control conditions, \( n \), equals the ratio of the preglomerular pressure fall to the total pressure fall from aorta to the intrarenal veins: 

\[ \frac{(p_a - p_e)/(p_a - p_c)}{p_e} \]

where \( p_e \) is the glomerular pressure and the subscript \( c \) refers to control conditions.

3. The radii of postglomerular vessels, i.e., efferent arterioles and peritubular capillaries, are assumed to be constant, independent of varying transmural pressure.

4. Furthermore, we assume that the force recorded by the tension receptor is proportional to the total circumferential wall tension per unit vessel length: 

\[ T = P \cdot r \]

where \( T \) is the transmural pressure difference and \( r \) is the internal radius. We prefer not to use the tension per unit wall thickness (\( P \cdot r/w \)), because variations in wall thickness resulting from varying \( r \) presumably do not alter the number of contractile or sensor elements in a cross section of the wall, and because the average tension obtained in this way may not reflect the tension at the sensor site. Instead, we will investigate the effect of interposing a wholly
compliant layer (intima and possible relaxed muscle fibers) between the lumen and the myogenically responsive fibers, giving a "wall tension radius" (R) greater than the "hemodynamic radius" (r). Under control conditions, the layer is assumed to be of uniform thickness along the tube. (In the kidney, with its increasing number of parallel vessels, tapered toward the efferent arteriole, the counterpart is a "passive layer" that decreases in thickness in proportion to vessel radius.)

5. In the control state, we assume that each vessel segment between the aorta and the glomerular capillaries has a muscle tone adjusted to its wall tension. Furthermore, the wall tension is assumed to be regulated by a closed loop gain of G, defined as the ratio of tension decline upon vessel constriction to the initial tension increase upon a step increase in transmural pressure P (Johnson and Intaglietta, 1976; Johnson, 1980):

$$G = \frac{P \cdot (r - r_c)}{(P_c - P) \cdot r_c}$$  (1)

where r, and r refer to radii at control (P_c) and altered transmural pressure (P), respectively.

Mathematical Development and Predictions

We assume that the Hagen-Poiseuille law applies for each infinitesimal segment along the tube:

$$F = -\frac{\pi dp}{8\eta dz} r^4(z)$$  (2)

F is the mass flux or "flow" through the tube, $\eta$ is the fluid viscosity, and z is a coordinate along the tube. Since the fluid is considered to be incompressible, F is a constant along the tube for each particular state of the tube. The inner radius r, and, obviously, the pressure p, vary with z.

We rewrite as

$$r^4(z) \frac{dp}{dz} = -f$$  (3)

where

$$f = \frac{8\eta F}{\pi}$$

Considering $\eta$ constant, f is proportional to flow. We shall refer to f also as "flow." We now introduce the myogenic response mechanism into Equation 3:

We assume that the tube has myogenic property along a certain fraction of its length from z = 0 to the site of glomerulus z = nL, where n is the fraction, 0 < n < 1. The location of glomerulus along z is considered of zero extension, and we therefore shall allow for discontinuity of radius of the tube at this point. From z = nL to z = L, we assume no myogenic response, and that this part of the tube has always the same inner radius, r_c, which is also the inner radius of the whole tube in the control state. A wholly compliant layer which separates lumen from the myogenic fibers is assumed to be incompressible. Thus, if R_c and R are the radii of the myogenically responsive wall layer in control state and an arbitrary state, respectively, then (cf. Fig. 2)

$$\pi(R_c^2 - r_c^2) = \pi(R^2 - r^2)$$

or:

$$r^2 = R^2 - (R_c^2 - r_c^2)$$  (4)

In Equation 1 for the closed loop gain, we let $r_c \rightarrow R_c$, $r \rightarrow R$, since the layer is assumed to be wholly compliant.

The transmural pressures in Equation 1 will be $p_c(z) - p_w$, and $p(z) - p_w$, where $p_w$, and $p_c$, are tissue pressures in control and altered states, respectively. To simplify the equations, we will hereafter refer to pressures relative to control tissue pressure as $p_c^\prime = p_c - p_w$, $p_i^\prime = p_i - p_w$, etc., as illustrated in Figure 3 (formally equivalent to assuming a control tissue pressure of 0). Then, we have from Equation 1,

$$R(z) = R_c \left(1 - G \frac{p_c^\prime(z) - p_w - p_i^\prime}{p_i^\prime(z) - p_c^\prime} \right)$$  (5)
FIGURE 2. Cross-section of tube model. $r = \text{inner radius}$ ("hemodynamic radius"), $R = \text{inner radius of myogenically responsive muscle layer}$. The interposed layer $R - r$ is assumed to be wholly compliant, but of constant volume, locating the stretching force of the whole transmural pressure ($P$) at $R$. Outer vessel circumference indicated by broken circle. Left: control state. Right: dilated vessel, with reduced $R - r$ (cf. Equation 4).

$p_c'(z)$ and $p'(z)$ vary along the tube, from $p_{ac}'$ and $p_{t}'$, respectively, at the tube entrance, to 0 and $p_{t}'$ respectively at the end of the tube.

In the control state, when the inner radius is uniform along the tube ($= r_c$), $p_c'(z)$ falls off linearly along the tube (Fig. 3) according to the forms

$$p_c'(z) = -\frac{p_{ac}'}{L} (z - L)$$

or, as follows from Equation 3,

$$p_c'(z) = -\frac{f_c}{r_c^3} (z - L)$$

where $f_c$ is flow. The perfusion pressure is $p_c'(0) = p_{ac}'$, and glomerular capillary pressure in the control state, $p_{c}'$, equals $p_c'(z)$ at $z = nL$.

In a varied state, with $p_{ac}' \neq p_{ac}'$ and $p_c' \neq 0$, the perfusion pressure is $p_c' - p_c'$. The change in transmural pressure will change the tube radius and the pressure profile in the region $z = 0$ to $z = nL$, as indicated schematically in Figure 3. From $z = nL$ to $z = L$, the pressure falls off linearly with a slope equal to $-f/r_c^4$, where $f$ is flow in the varied state. Conti-

guity of pressures through the glomerulus is essential in our model, and therefore the curve from $z = nL$ to $z = L$ must connect the pressure curve from $z = 0$ to $z = nL$ at the site of the glomerulus. The governing equation for $p'(z)$ from $z = 0$ to $z = nL$ is Equation 3 combined with Equations 4 and 5, which gives the one equation

$$R_c^2 \left( 1 - G \frac{p'(z) - p_c' - p_c'(z)}{p'(z) - p_c'} \right)^2 - (R_c^2 - r_c^2)^2$$

This equation we solve for $p'(z)$ subject to the conditions:

$$p'(0) = p_{ac}'$$

$$p'(nL) = p_{t}' = (f/r_c^4)L(1 - n) + p_{t}'$$

The last condition describes the postglomerular pressure drop and connects $p'$ to the straight-line segment of Figure 3 at $z = nL$.

Equation 7 and conditions 8 and 9 are the mathematical formulation of our model. From this formulation, we shall derive $p'(z)$ and the inner tube radius $r(z) = R - r$, along the tube, together with the dependence of flow $f$ on both aortic pressure, $p_{ac}'$, and on tissue pressure, $p_{t}'$, for various choices of $G$, $n$, and $R_c$. We keep $L$, $p_{ac}'$, and $r_c$ fixed throughout. The gain factor is assumed not to vary along the tube from $z = 0$ to $z = nL$.

Equation 7 is an ordinary (nonlinear) differential equation of first order of a type which can be transformed into an integrable form. However, in the general case, the integrals are difficult to evaluate, and we then instead solve the equation subject to conditions 8 and 9 numerically on a computer. For one special, but important, case, we integrate quite easily and can present formulas.

The Case, $G = 1$, $R_c = r_c$

In this case, Equation 7 and condition 8 give, cf. Appendix 1

$$p'(z) = p_{ac}' + (L - z)/(L/(p_{ac}' - p_c'))^3$$

$$- f L/(r_c^4 p_{ac}'^2)(L - z)^3 + f L r_c^4 p_{ac}' - f L r_c^4 p_{ac}'^3/3$$

Using the last condition, 9, we get the equation

$$f L(1 - n) + p_{ac}' = p_{ac}' + L(1 - n)/(L/(p_{ac}' - p_c'))^3$$

$$- f L r_c^4 p_{ac}'^2 L(1 - n)^3 + f L r_c^4 p_{ac}'^3/3$$

The Case, $G = 1$, $R_c = r_c$. The last condition gives the equation

$$f L/(r_c^4 p_{ac}'^2)(L - z)^3 + f L r_c^4 p_{ac}' - f L r_c^4 p_{ac}'^3/3$$

The Case, $G = 1$, $R_c = r_c$.
which we solve with respect to $p_a' - p_t'$

$$p_a' - p_t' = p_a' (1 - n) \frac{f}{f_c} \left[ \frac{1}{(1 - (f/f_c))^3 (1 - (1 - n)^3)} \right]^{1/3}$$

(12)

Here, we have taken account of the relation

$$f_c = r_c^2 \frac{P_{ac}}{L}$$

(13)

which follows from Equations 6 and 6'.

Effect of Varying Aortic Pressure ($p_a'$)

Equation 12 gives the relation between perfusion pressure $p_a' - p_t'$ and flow $f$, and Figure 4a shows this dependence of $f$ on $p_a'$ when $p_t' = 0$ for three values of $n$: $n = 0.4$, $n = 0.5$ and $n = 0.6$. Since control radius ($r_c$) is equal proximal and distal to glomerulus, varying $n$ does not affect control flow. We have therefore scaled the flow and pressure so that $f_c = 1$ and $p_a' = 1$. Equation 12 shows that when $p_t' > 0$, i.e., at tissue pressure above control level, the curves are simply translations of the ones shown by a distance $p_t'$ to the right. This is a property holding, in general, for similar curves.

In all three cases on Figure 4a, the autoregulation is good, but significantly better for high than for low $n$-values. This means that autoregulation of flow is favored by a high control preglomerular resistance fraction ($n$). Figure 4a also indicates that when $G = 1$ the flow approaches asymptotically an upper limit with increasing perfusion pressure. This upper limit $f_{ul}$ is given by the formula

$$f_{ul} = f_c \frac{1}{[1 - (1 - n)^3]^{1/4}}$$

(14)

Our model, in this case, does not account for a further increase of flow for high perfusion pressure, because the tube radius will decrease toward zero with increasing perfusion pressure in such a way as to regulate the flow completely. This is not the case when the gain factor is less than one, as we shall see in the next section.

Figure 4, b-d, shows pressure and radius changes along the tube at four different aortic pressures, and for the same values of $n$ as used in the pressure-flow curve in Figure 4a. Corresponding curves on each

![Figure 4](http://circres.ahajournals.org/)

**Figure 4.** Effect of varying aortic pressure, $p_a'$, on flow (Fig. 4a), pressure and inner radius along the tube (Fig. 4b–d) at three different values of preglomerular resistance fraction ($n = 0.4$, $0.5$, $0.6$). Gain factor $G = 1$, $R_c = r_c$, i.e., "wall tension radius" equals "hemodynamic radius". Aortic pressure, radius, and flow scaled to 1 in control situation, and $L = 1$. Corresponding pressure and radius curves are indicated by numbers equal to flow ($f$).
The figures are identified by numbers indicating flow according to Equation 12. L has been scaled to 1. The other parameters are scaled as in Figure 4a, and $p_t = 0$. When $p_t > 0$, the given pressure curves represent $p'(z) - p_t'$ while the $r(z)$ curves are unchanged. The figures show that the first part of the tube reacts most strongly to both increased and reduced aortic pressure, and that positions close to the glomerulus, i.e., the late parts of the afferent arteriole, participate little in autoregulation at moderate variations of aortic pressure. This is demonstrated more explicitly in Figure 5, showing vessel radii at three different preglomerular sites ($z = 0.2, 0.4, 0.6$) as functions of aortic pressure. At $z = 0.4$, which may represent the middle of the afferent arteriole (cf. Fig. 1), there is little dilation until aortic pressure is lowered by more than $30\%$ of control. As also illustrated in Figure 5 (lower panel), luminal pressure shows an increasing degree of autoregulation when approaching the glomerulus ($z = 0.6$). In fact, it follows from the assumption of constant postglomerular radius that glomerular pressure will be autoregulated exactly in proportion to blood flow (cf. Equation 9). The same applies to pressure at any postglomerular level.

The very marked increase of $r(z)$ at low $p_t'$ deserves some comments. Clearly, any value of $r(z)$ exceeding $1.5r_c$ at low transmural pressure seems unlikely because of passive resistance to excessive elongation by connective tissue and by the muscle cells themselves. To investigate the effect of this "unphysiological" property of the model, we have arbitrarily assumed upper limits for $r(z)$ of $1.5r_c$ and $1.2r_c$ and built this into Equation 7. Equations 7, 8, and 9 are still integrable when $G = 1$, $R_c = r_c$. Figure 6 shows that this modification of the model clearly impairs autoregulation at aortic pressure less than $60\% - 70\%$ of control, and causes a sharper break in the pressure-flow curve. However, the slope of the curve around control aortic pressure remains practically unchanged.

A further variation of the model that also modifies the high pressure part of the pressure-flow curve is to take account of both the passive and active force of the vascular smooth muscle in the walls. (Gow, 1980; Murphy, 1980). For lack of direct measurements on renal blood vessels, we simply model the tube radius...
as a function of pressure for any segment (i.e., any $z$) along the preglomerular part of the tube as in Figure 7a. Around control pressure, we have a myogenic response and the curve is part of a hyperbola. For lower pressures, this curve switches over to the curve due to the passive force modeled here as above as a constant radius curve. For high pressures, the wall contraction first stops due to a fall in active force at extreme shortening of the muscle fibers, and radius then maintains a constant value up to a still higher critical pressure where there is a sudden increase in radius when the active force "gives up" and the passive force takes over. This variation of radius we build into Equation 7, which then is solved subject to conditions 8 and 9 when $G = 1$ and $R_c = r_c$. For values of radii as indicated in Figure 7a, and $n = 0.6$ and with the rest of parameter values as before, Figure 7b shows the resulting pressure flow curve. The marked increase in flow when segments gradually "give up" the active "phase" is clearly reflected in Figure 7c showing variation of pressure and radius along the tube for aortic pressures around the critical value.

**Effect of Varying Tissue Pressure**

Figure 8 shows the effect on flow of increasing tissue pressure (and intrarenal venous pressure) above control level ($p'_t > 0$) at unchanged aortic pressure

![Figure 8](image-url)
In spite of the linear reduction of perfusion pressure \((p_a' = 1)\), there is little reduction of flow at tissue pressures less than one-third of aortic pressure. Furthermore, flow is better maintained when the control preglomerular resistance fraction \(n\) is high (e.g., \(n = 0.6\) vs. \(n = 0.4\)). Also, these flow curves will show a sharper breaking point if dilation is limited, as shown for \(n = 0.6\) by the broken lines.

### The General Case

Equation 7 is solved numerically on computer, using the improved Euler method (Braun, 1978). For each value of \(p_a'\) from condition 8, the flow parameter \(f\) is varied so that condition 9 is fulfilled within a tolerable degree of accuracy.

Since \(R_c > r_c\) in the general case, Equation 7 is singular when \(p_a' - p_t'\) increases above a certain value, dependent on the parameters of the equation. This singularity is connected to the inner radius \(r(z)\) which becomes 0 at \(z = 0\) when \(p_a' - p_t'\) grows. Since we here do not intend to describe this blocking of the tube in detail, we stop calculations when inner radius becomes less than 0.3 at any point along the tube (compared to 1 in control state).

In our calculation, we have focused on demonstrating some effects by varying parameters according to Table 1. We have set \(f_c = 1, p_{ac}' = 1, L = 1, r_c = 1\).

Figure 9a-c, shows \(f\) as a function of \(p_a'\) at values of \(n = 0.5, 0.6,\) and 0.4, and for a \(p_t'\) of 0. (Translation a distance \(p_t'\) to the right when \(p_t' > 0\).) The dashed curves are the corresponding curves (same \(n\)) in Figure 4a, i.e., the pressure flow relationship observed with a gain factor \(G = 1\) and a "wall tension radius" \(R_c = r_c\). Relative to this condition, Figure 9a shows somewhat impaired autoregulation when \(G\) is reduced to 0.7 (curve no. 1), whereas flow is maintained better at both increased and reduced aortic pressure when the "wall tension radius" is increased to 1.2 (curve no. 2). The latter effect is also demonstrated by curve no. 3 in Figure 9b, where the combination of \(R_c = 1.2, G = 1\), and a high control preglomerular resistance fraction \((n = 0.6)\) gives the most perfect autoregulation of all curves shown. As shown in Appendix 2, "superautoregulation", i.e., a rise in flow at reduction of aortic pressure is not possible for any combination of model parameters. Curve no. 4 (not drawn separately) is practically identical to the dashed one \((G = 1, R_c = r_c = 1)\), showing that the effect of reducing the gain factor to 0.7 is compensated by rising the control "wall tension radius" to 1.2. The comparatively weak autoregulation shown in Figure 9c results from a low control preglomerular resistance fraction \((n = 0.4)\), and again the improvement in autoregulation caused by \(R_c: 1 \rightarrow 1.2\) (curve no. 5) is offset by a reduction of \(G\) to 0.7.

### Table 1

<table>
<thead>
<tr>
<th>Curve no.</th>
<th>(r_c)</th>
<th>(R_c)</th>
<th>(L)</th>
<th>(n)</th>
<th>(p_{ac}')</th>
<th>(p_t')</th>
<th>(G)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0.5</td>
<td>1</td>
<td>0</td>
<td>0.7</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1.2</td>
<td>1</td>
<td>0.5</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>1.2</td>
<td>1</td>
<td>0.6</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>1.2</td>
<td>1</td>
<td>0.6</td>
<td>1</td>
<td>0</td>
<td>0.7</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>1.2</td>
<td>1</td>
<td>0.4</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>1.2</td>
<td>1</td>
<td>0.4</td>
<td>1</td>
<td>0</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Symbols: \(r_c = \) inner "hemodynamic" radius in control; \(R_c = \) "wall tension" radius in control; \(L = \) tube length; \(n = \) position of glomerulus; \(p_{ac}' = \) control aortic pressure; \(p_t' = \) tissue pressure; \(G = \) feedback gain factor.
Pressure and radius curves as functions of \( z \) (as in Fig. 4, b–d) have also been worked out for the parameters shown in Table 1, but are not shown here. In general, a reduction of \( G \) causes smaller changes in \( r \) and greater changes in pressures at all values of \( z \) from 0 to \( nL \). An increase of \( R_c \) causes the opposite effect.

In Figure 10, we relate flow to tissue pressure, \( p'_t \), at unchanged aortic pressure (\( p'_a = 1 \)) for the same values of parameters as used in Figure 9, and again we have numbered the curves according to Table 1. The maintenance of flow at increasing \( p'_t \) above control level (\( p'_t > 0 \)) varies considerably with choice of parameters, in general in the same manner as maintenance of flow at changes in aortic pressure. Thus, with the optimal parameters tested here (curve 3: \( R_c = 1.2, G = 1, n = 0.6 \)), there is less than 5% reduction of flow when tissue pressure is increased to 50% of aortic pressure.

**Discussion**

In the present model, we simplified the complex renal system of parallel and series resistances to a straight tube, i.e., to a system of series resistances. This is valid only if the various parallel channels have similar pressure-flow relationships, i.e., if autoregulation of blood flow is equally well developed in deep and superficial layers of the kidney. Data from the literature are conflicting on this point: Using the albumin transit time technique, Thurau et al. (1960) found poor autoregulation in the renal medulla of dogs, whereas Grangsj0 and Wolgast (1972) reported good autoregulation, in agreement with local \( H_2 \) gas washout in the outer medulla (Aukland, 1967). Inert diffusible tracer techniques also have shown similar autoregulation in deep and superficial layers of the cortex (Leyning, 1971; Clausen et al., 1980; Hope et al., 1981). In contrast, uptake of microspheres indicates a rise in inner cortical flow and a fall in outer cortical flow at reduced arterial pressure (e.g., McNay and Abe, 1970). A greater increase in deep than in superficial microsphere uptake is consistently elicited also by other vasodilatory stimuli, such as increased ureteral pressure and intraarterial infusion of vasodilators such as acetylcholine, bradykinin, prostaglandin \( E_2 \), dopamine, etc. (ref. in Aukland, 1976). However, a series of experiments in our laboratory, including comparison of the uptake of microspheres of various diameters and simultaneous uptake of \(^{125}\)I-iodoantipyrine (Clausen et al., 1980, 1981) as well as in vitro studies of skimming (\( \text{Ofjord et al., 1981; \( \text{Ofjord E.S., and Clausen G., personal communications}) \), suggest that the "redistribution" of microsphere uptake during vasodilation mainly reflects reduced skimming of microspheres at the origin of the deep afferent arterioles, secondary to increased diameter of the interlobular arteries. In sum, the assumption of similar pressure-flow curves in deep and superficial layers seems reasonably well supported by experimental data.

The assumed localization of the wall tension regulation to preglomerular vessels was based on a large body of experimental data indicating that the major autoregulatory resistance changes are located upstream from the glomeruli. In fact, micropuncture studies in rats suggest opposite postglomerular resistance changes at lowered pressure (Brenner et al., 1974). It may be noted, however, that a tension regulation also in the efferent arterioles would improve autoregulation of blood flow, but would probably impair autoregulation of glomerular capillary pressure at large changes of arterial pressure.

The main assumption for the present model, the existence of a tension regulation in renal arterial/arteriolar smooth muscle, has not been proven experimentally. As reviewed by Johnson (1980), some isolated vessels show contractile responses to stretch, but seem to give no direct evidence for a tension regulation. On the other hand, a number of in vivo observations on peripheral vessels are difficult to explain without postulating a myogenic response. In the case of the renal blood vessels, the observation that preglomerular diameter changes inversely to changes in transmural pressure in a kidney transplant without juxtaglomerular apparatus (Gilmore et al., 1980) provides strong evidence for a myogenic response.

Obviously, our mathematical model cannot prove the assumption of a tension regulation, but it can elucidate the pressure-flow relationship that would result if such a mechanism does exist. More specifically, the model enables us to decide whether a wall tension regulation can be excluded, as has been claimed previously (Thurau, 1967). In the following, we will therefore briefly compare the model predictions to experimental pressure-flow data, and point...
out other data that tend to support or contradict the model.

At moderate reductions of aortic pressure, the model predicts satisfactorily the maintenance of flow, and the corresponding radii and segmental pressures show clearly the "descending" nature of the myogenic autoregulation, as predicted by Kilii (1975, 1981) and Johnson (1980). Even with a closedloop feedback gain of 1, there is no "superautoregulation," i.e., increased flow at reduced aortic pressure. If one assumes that the sensor determining myogenic tone is located within the vessel wall and separated from the lumen by a layer that offers no resistance against dilation, the autoregulation is improved, but it is still not "super." Thus, the finding of increased renal blood flow at reduced aortic pressure in some experiments in dogs (Hall et al., 1977) clearly requires some dilatory mechanism in addition to the wall tension regulation.

At more severe reduction of aortic pressure—i.e., half control value or lower—the maintenance of constant wall tension gives clearly higher flow than that observed experimentally. However, the associated increase of proximal radii by 2-3 times is clearly unrealistic. It is therefore interesting to note that the arbitrary introduction of a maximal radius increase of 50 or 20% gives the pressure-flow curve a more familiar shape, including a relatively sharp "lower limit of autoregulation" (Fig. 6). Since apparently complete relaxation of vascular smooth muscle, induced for instance by intra-arterial infusion of acetylcholine, rarely increases renal blood flow to more than twice that of control, a maximal increase of radii by a factor of 1.2 would seem to be the most realistic (according to Poiseuille: \( V \sim 1.2 \)).

At increased arterial pressure, the model with myogenic response only fails to show an upper limit for autoregulation, i.e., flow remains practically constant in spite of excessive pressure elevations. An obvious explanation to this fault is that the model neglects the fall in smooth muscle contractile force with marked shortening of the fibers. A modification of the model as that leading to the results in Figure 7 may well simulate the real situation. It should be noted, though, that practically unchanged renal blood flow was observed by Thurau and Kramer (1959), at arterial pressures up to 300 mm Hg in the dog. (Corresponding data for other species seem not available.) If so, the myogenic model mimics experimental data also at physiologically reasonable elevations of aortic pressure.

The "lower limit of autoregulation" is reduced and the "breaking point" is sharper with a high than with a low control preglomerular resistance fraction \( n \), reflecting that a greater fraction of the renal vascular resistance is subject to autoregulation. Thus, a low glomerular pressure relative to aortic and tissue pressures in the control situation will favor autoregulation at large reductions of aortic pressure. Since our definition of the preglomerular resistance fraction excludes the pressure drop in the "vascular waterfall," a realistic estimate of the ratio requires knowledge of the normal "tissue pressure." Whereas the interstitial fluid pressure in the dog kidney is only of the order of 5 mm Hg, intrarenal venous pressure measurements suggest a "total tissue pressure" of 15 to 20 mm Hg (ref. in Ofstad and Aukland, 1983). If this is a relevant figure, then \( n \) would be 0.55-0.60 even with a glomerular pressure as high as 60 mm Hg.

An equal increase of tissue pressure and intrarenal venous pressure, as may be approximated by ureteral or venous stasis, causes descending dilation of the preglomerular vessels, and flow is maintained reasonably constant. However, the model does not predict a rise in blood flow as observed in some studies (Navar, 1978). Again, one might suspect some additional dilatory mechanism at increased ureteral pressure, and experimental data clearly point to prostaglandin E2 (Blackshear et al., 1979).

It may be noted, in this connection, that the present model does not include changes in tissue pressure secondary to changes in aortic pressure. Whereas such a relationship might be built into the model, it would probably not cause large changes in the predicted pressure-flow curves.

A rather specific prediction of the model is the succession of resistance changes, namely, primary involvement of proximal vessels and appreciable resistance changes in the last preglomerular segments only at large pressure changes. This prediction agrees well with the finding that the pressure in the terminal portions of the interlobular arteries of the rat kidney is autoregulated (Kallskog et al., 1976; Tønder and Aukland, 1979). In fact, in more recent experiments, where it was assumed that flow in the punctured interlobular artery varied in proportion to total renal blood flow, the resistance of the interlobular arteries (+ larger arteries) fell by about 50% when arterial pressure was reduced by 15-25 mm Hg, while combined afferent/efferent arteriolar resistance showed little change (Tønder, K.H., personal communication). This "descending dilation" seems hardly compatible with the tubuloglomerular feedback, which would be expected to exert its main effect close to the macula densa, i.e., in the terminal portions of the afferent arterioles. Admittedly, an increased tubular formation of adenosine at increased filter load, as recently proposed by Spielman and Thompson (1982), might give a "descending autoregulation," provided that adenosine has a more pronounced vasoconstrictor effect on the interlobular arteries than on the afferent arterioles.

The present model provides autoregulation of glomerular capillary pressure in proportion to flow. Since the glomerular filtration rate (GFR) depends on both glomerular pressure and plasma flow, (Brenner et al., 1974), it follows that GFR will be autoregulated less well than blood flow. More quantitative predictions of GFR regulation could well be obtained by combining the present model with a model of glomerular ultrafiltration, preferably taking into account also variations in proximal tubular pressure (Jensen et al., 1981).
Any degree of renal arterial pressure reduction causes increased renin release. However, as suggested by Kiil and coworkers (Eide et al., 1973; Kiil, 1975), the greatly accelerated renin release observed when aortic pressure approaches the lower limit of autoregulation might indicate that appreciable dilation of the distal part of the afferent arteriole (where the renin-secreting cells are located) is not elicited by less severe pressure reduction. This hypothesis agrees well with the “descending” nature of autoregulation demonstrated in the present model. (cf, e.g., Fig. 5).

In the present study, we have chosen model parameters to fit the kidney where the site of autoregulation is reasonably well established. Nevertheless, there is evidence for myogenic autoregulation, also, in other organs, and the present model might well be adaptable. Obviously, a mathematical model cannot prove the importance or even existence of a myogenic tension controller, but it may be helpful in giving predictions that can be tested experimentally.

### Appendix 1

**Derivation of Equation 11**

When \( G = 1 \) and \( R_c = r_c \), Equation 7 reduces to

\[
\frac{r_c}{L^4} \left( \frac{p_c'(z)}{p'(z) - p_t'} \right) \frac{dp'}{dz} = -f. \tag{15}
\]

Substituting \( p_c'(z) \) from Equation 6, we further get

\[
\frac{r_c}{L^4} \frac{p_{ac}^4}{(p'(z) - p_t')^4} \frac{dp'}{dz} = -f
\]

which can be rearranged as (“separation of variables”)

\[
\frac{dp'}{(p' - p_t')^4} = -\frac{fL^4}{r_c p_{ac}^4 (L - z)^4} \frac{dz}{dz}
\]

We integrate left- and righthand sides with respect to \( p' \) and \( z \), respectively:

\[
-\frac{1}{3} \left( p' - p_t' \right)^3 = -\frac{fL^4}{r_c p_{ac}^4 (L - z)^3} + \frac{C}{3}.
\]

Here, \( C \) is an integration constant. Solving with respect to \( p' \), we get

\[
p'(z) = p_t' + \frac{L - z}{(C(L - z)^3 + fL^4/r_c p_{ac}^4)\frac{1}{3}} \tag{16}
\]

C will be specified imposing Equation 8:

\[
p_{ac}' = p_t' + \frac{L}{(C(L - z)^4 + fL^4/r_c p_{ac}^4)^{\frac{1}{3}}}
\]

Thus,

\[
C = \frac{1}{(p_{ac}' - p_t')^3} - \frac{fL}{r_c^4 p_{ac}^4}
\]

Substituting this expression for \( C \) into Equation 16, we get Equation 11.

### Appendix 2

**Super-autoregulation**

With super-autoregulation, we mean either flow higher than control flow for perfusion pressure lower than control value, or flow lower than control flow for perfusion pressure higher than control value, or both, cf. Figure 11a (we have chosen \( p_t' = 0 \)). For this to be possible, pressure curves like the ones in Figure 11b must exist. The curve starting at \( p_{ac}' < p_{ac} \) must cross the control pressure curve for the corresponding flow to be higher than control value, and the curve starting at \( p_{ac}' > p_{ac} \) must also cross the control pressure curve for flow to be lower than control value. We show that such crossing is impossible from Equation 7. For assuming the curve for \( p'(z) \) crosses the \( p_c'(z) \) curve at \( z = z_0 \) (\( p'(z_0) = p_c'(z_0) \)). At \( z = z_0 \), Equation 7 then becomes (\( p_t' = 0 \))

\[
\frac{r_c}{L^4} \frac{dp'}{dz}(z_0) = -f
\]

or:

\[
\frac{dp'}{dz}(z_0) = -f/r_c^4.
\]

For the case, \( p_{ac}' = p_{ac} \), therefore, \( \frac{dp'}{dz}(z_0) < -f/r_c^4 \), since \( f > f_c \) for this curve, but we should have \( \frac{dp'}{dz}(z_0) \geq -f/r_c^4 \) for crossing. Hence, the crossing
assumption is false. The case when $p_0' = p_0'' > p_c'$ is handled similarly. The conclusion holds for all possible choices of G, whether a constant value or variable value along the tube. When $p_0' > 0$, it is the crossing between the curves $p'(z) - p_c$ and $p(z)$ that is impossible. Thus super-autoregulation is not possible in this model.

References


Bayliss WM (1902) On the local reactions of the arterial wall to hemorrhage. Arch Physiol 2: 77-93


(Or) Am J Physiol: Renal Fluid Electrolyte Physiol 3: F357-F370


Thurau KWC (1964) Autoregulation of renal blood flow and glomerular filtration rate, including data on tubular and peritubular capillary pressures and vessel wall tension. Circ Res. 14/15 (suppl 1): 131-141


Tonder KH, Aukland K (1979) Interlobular arterial pressure in the rat kidney. Renal Physiol (Basel) 2: 214-221


Circulation Research/Vol. 52, No. 3, March 1983

Downloaded from http://journals.ahajournals.org/ by guest on July 11, 2017
A mathematical analysis of the myogenic hypothesis with special reference to autoregulation of renal blood flow.
A H Oien and K Aukland

doi: 10.1161/01.RES.52.3.241

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1983 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/52/3/241

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation Research_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation Research_ is online at:
http://circres.ahajournals.org/subscriptions/