PREVIOUS REPORTS have accounted for autoregulation of renal blood flow on the basis of increases in extravascular pressure1-4 which act as compressing forces on the renal vascular bed. Renal tissue pressures ranging between 2 and 120 mm Hg have been found to approximate closely the pressures in deep renal veins of a caliber exceeding 0.73 mm diameter.5 As a result of these investigations, the concept has been developed that the major driving force for blood flow through the mass of kidney tissue is the difference in pressure between the renal artery and the deep intrarenal veins, which includes virtually all of the renal substance.5 Another important component of resistance is the contribution of Bowman capsular extravascular pressure to autoregulation by virtue of its additive effect to the generalized renal interstitial pressure.2 It has been proposed that the net sum of these extravascular forces not only serves to maintain the renal blood flow within narrow but variable limits but, by means of a local feedback, accounts for the regulation of the glomerular filtration rate. The mechanism of autoregulation is accounted for primarily on the basis of rising intrarenal venous pressures, the "prevenous" resistance being relatively constant through the autoregulatory range.5

Earlier workers, including Winton,5,6 among others,7,8 have rejected or discounted the tissue-pressure theory of autoregulation, and a recent report by Waugh10 has attempted to invalidate this explanation of autoregulation on the basis of recorded tissue pressures and intrarenal venous pressures that purport to show that the major increase in renal resistance through the autoregulatory range is in the prevenous segment. In the course of recent work in our laboratory, it was found that tissue pressures and intrarenal venous pressures are difficult measurements from a technical standpoint and that experimental artifacts are easily obtained that result in erroneous segmental resistance calculations.11

The main purpose of the present investigation is to clarify some of the major experimental difficulties in the measurement and interpretation of the various intrarenal pressures. The results provide further evidence for the causal role of the renal extravascular pressure in the autoregulation phenomenon.

Methods

Eighteen dog kidneys were perfused with homologous heparinized blood at 36 to 37 C. by means of a heart-lung perfusion apparatus previously described.12 A urine flow meter was inserted into the circuit so that urine flow rate was continuously monitored and recorded on a Sanborn direct-writing recorder. Kidneys were transferred to the heart-lung apparatus without interruption of renal blood flow or urine flow. Urine flows ranged from 0.5 to 9.0 cc./min. Kidneys were perfused at a constant renal-artery pressure by means of a Starling shunt mechanism and continuously weighed on a strain-gauge weighing device.13 Intrarenal venous pressures were measured by retrograde catheterization* as previously reported,3 and tissue pressures were determined in several experiments as described in an earlier paper.1 In several experiments mannitol was used to produce a diuresis and the ureter was progressively occluded or totally clamped according to procedures reported by others.14 and renal segmental resistances were calculated.3,4

Results

The following figures are representative examples of the perfusion experiments carried out in this study. Figure 1 illustrates the results from an isolated kidney perfused at constant renal-artery pressure. A variety of

*Position of catheter tips was determined at termination of experiments.
intrarenal venous pressures are obtained depending on the depth of the measuring catheter. The depth of the venous catheter in the renal substance is indicated above the upper frame of the figure. Venous pulsations are noted which characteristically disappear when the catheter is withdrawn from the kidney substance and emerges into the external renal vein. The figures at the lower portion of the record indicate that the calculated intraorgan resistance (\( \text{RA-RV}_{\text{int}}/F \)) differs greatly depending on the catheter depth. When the calculated venous component of resistance is progressively decreased by catheter withdrawal, the intraorgan resistance appears to increase. This figure emphasizes the importance of the position of the catheter tip in the intrarenal venous segment.

Figure 2 presents data obtained from an isolated perfused kidney and shows the appearance of a common artifact which ensues in the absence of suitable precautions, i.e., if the intrarenal venous catheter is not adequately secured in position, when the renal-artery pressure is increased, the catheter slips downstream owing to the increased velocity of the venous effluent. It may be noted that although the overall resistance (\( \text{RA}/F \)) rises when the arterial pressure is increased (bottom of figure), the calculated, correctly obtained, intraorgan resistance (\( \text{RA-RV}_{\text{int}}/F \)) actually falls with a rise in arterial pressure. This figure therefore emphasizes a crucial feature in the technique of intrarenal venous-pressure measurement.

Figure 3 displays the raw data and resist-
Isolated perfused kidney illustrating the relationship of deep intrarenal venous pressure and renal-artery pressure (kidney weight, 45 Gm.). Note the slippage of the catheter (upper frame) after elevation of renal-artery pressure and its effect on calculated intraorgan renal resistance (lower figures). (Zero reference points, at midpoint of kidney shown on both arterial and venous recordings. Urine flow is obtained by multiplying 1.5 X tangent of the angle.)
MECHANISM OF AUTOREGULATION

Figure 3
Isolated perfused kidney showing the effect of the depth of the tip of the intrarenal venous catheter on calculated intraorgan renal resistance (kidney weight, 33 Gm.). $RV_1 =$ venous pressure measured from the catheter tip in the arcuate vein. $RV_2 =$ venous pressure measured from the catheter tip in the interlobar vein. Figures at the upper part of the record indicate that attenuation is altered between a full pressure scale of 0 to 100 and 0 to 200 mm. Hg. (Arterial pressures taken at 0 to 200, and venous pressures at 0 to 100 mm. Hg.)

Discussion
Mechanism of Autoregulation
Previous misunderstandings have arisen regarding the significance of renal-tissue pressure and of intrarenal venous pressures as they relate to the autoregulation phenomenon. The results of this study have served to clarify the role of intrarenal venous pressures in the mechanism of autoregulation. The findings of this investigation have confirmed the results of previous reports.1-4 It is proposed that, as the renal-artery pressure is increased into the lower range of autoregulation (60 to 100 mm. Hg), renal tubular pressure and interstitial...
pressures rise; these are correlated with the first appearance of urine and the secondary prolonged increase in kidney weight. The effect of the sum of these extravascular pressures is to compress the capillaries and intrarenal veins of the kidney, resulting in a rise in overall renal vascular resistance (autoregulation). An exceedingly interesting observation has been the variety of intrarenal venous pressures, which differ greatly according to anatomical location and renal-artery pressure. The large differences in these pressures can probably be accounted for on the basis of the presence of stenoses and sinusoidal cushions, which have been described by the excellent work of Koester, Locke, and Swann. These latter structures may play a significant role in throttling down the flow of blood through the intrarenal venous segment, and their effects may be greatly enhanced by a rise in extravascular pressure.

It is seen that when the venous component of resistance is removed by the calculation of intraorgan resistance \( RA - RV_{int} / F \), there is little change in resistance through the autoregulatory range, i.e., the major component of resistance has been unmasked. Other possible components of resistance have been discussed in a previous report from this laboratory. The findings of the present study further substantiate the tissue pressure theory of autoregulation, which has also been corroborated by the work of others.

Critical Features of Intrarenal Venous Pressure Measurement

If intrarenal venous pressure measurements are to replace tissue pressures, much caution needs to be observed in their measurement. Intrarenal venous catheters should be advanced into the interlobular region, if possible, and secured in place so that changes in blood flow will not dislodge them. The various other important criteria should also be followed in order to obtain valid pressure measurements. It is probably not possible to obtain a venous-wedge pressure because of the extensive degree of venous collaterals. The possible effect of the catheter in obstructing venous outflow, thereby resulting in falsely high venous pressures, is unlikely for the above reasons and also because of the observation that the greater the degree of autoregulation (i.e., the less the change in blood flow with a change in arterial pressure) the higher does the intrarenal venous pressure increase. The results of the present study are considered adequate to account for the artifacts obtained by Waugh in his recent report on the measurement of intrarenal venous pressure.

Effect of Ureteral Occlusion

The results of ureteral occlusion obtained in the present study and by others have differed greatly from those of Malvin, Wilde, and Sullivan. Investigations undertaken in our laboratory have revealed that, when ureteral pressure exceeds resting tissue pressure, renal blood flow decreases significantly. Total ureteral occlusion results in a greatly decreased renal blood flow and a significant rise in overall renal vascular resistance. Tubular
MECHANISM OF AUTOREGULATION

pressure increases are transmitted to the intrarenal venous segment and produce a marked increase in venous segment resistance. Results obtained with ureteral-pressure elevation in this study and others corroborate the role of extravascular pressure in the autoregulation of renal blood flow.

Physiological Significance of Renal Autoregulation

Previous work in this laboratory has shown that when kidneys exhibit no autoregulation, the renal blood flow becomes exceedingly large at high renal-artery pressures. In one such study, when the renal-artery pressure was increased from 80 to 180 mm Hg, the renal blood flow increased from 1 to 9 cc./min./Gm. of kidney weight, and the tissue pressure rose only slightly. A kidney in this situation is acting as a large low resistance arteriovenous shunt, which carries progressively larger flows at higher arterial pressures. Autoregulation would appear, therefore, to perform a role in the total body economy.

Mechanism of "Pressure Diuresis"

The results of previous investigators have not shown this rise in tissue pressure and intrarenal venous pressure as a response to an increase in renal-artery pressure. Other investigators have not therefore attempted to show a causal relationship between a rise in peritubular capillary pressure and an increase in urine flow when the renal-artery pressure is increased (glomerular filtration rate constant). However, the results of the present study and other investigations carried out in this laboratory open the possibility that the mechanism of hydrostatic pressure diuresis can be explained on the basis of an increase in peritubular capillary pressure. Further work is needed to evaluate this possibility.

Role of the "Myogenic Reflex" in the Autoregulation Phenomenon

The myogenic theory of Bayliss has been invoked to explain the autoregulation of flow in the kidney. Numerous objections to this theory have already been raised. Previous reports have explained the mechanism of autoregulation in the complete absence of a myogenic reflex. The fact that kidneys showing the greatest degree of autoregulation also exhibit the greatest increases in tissue pressure cannot be explained on the basis of the myogenic theory. According to this latter theory, kidneys showing the largest increase in resistance in response to an elevation of renal-artery pressure should show the smallest increase in tissue pressure. The secondary prolonged increase in kidney weight coincident with the development of a rise in resistance cannot be adequately explained on the basis of the Bayliss response. As a matter of fact, injections of exceedingly small amounts of epinephrine (0.01 to 0.1 µg.) into the renal arterial inflow result in an increase in afferent arteriolar resistance and a marked decrease in kidney weight, tissue pressure, and intrarenal venous pressure. These latter responses in pressure and kidney weight are exactly the

Figure 5

Isolated perfused kidney showing the effects of partial and total ureteral occlusion and increased renal-artery pressure on renal blood flow, tissue pressure, intrarenal venous pressure, resistances, and urine flow (kidney weight, 35 Gm.). Note the legend on the second frame from the bottom denoting the types of resistances calculated.
Figure 6

Model and diagrammatic representation of arterial-venous pressure relationships in the isolated kidney. The group of venous pressures in italics are associated with the arterial pressure of 80 mm. Hg and those in roman, with arterial pressures of 180 mm. Hg (stenoses and sinusoidal cushions are not shown in the diagram). Calculations of over-all and intraorgan vascular resistances are shown at the bottom of the figure.

<table>
<thead>
<tr>
<th>Renal Artery Pressure (mm Hg)</th>
<th>Renal Vein Pressure (mm Hg)</th>
<th>Renal Blood Flow (cc/min)</th>
<th>Intrarenal Venous Pressure (mm Hg)</th>
<th>Over-all Renal Resistance (mm Hg/cc/min)</th>
<th>Intrarenal Resistance (mm Hg/cc/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>80</td>
<td>0</td>
<td>100</td>
<td>8</td>
<td>80.80 = 0.80</td>
<td>80.80 - 0.72 = 0.72</td>
</tr>
<tr>
<td>180</td>
<td>0</td>
<td>139</td>
<td>80</td>
<td>180.80 = 1.29</td>
<td>180.80 - 0.72 = 0.72</td>
</tr>
</tbody>
</table>

Reverse of what is obtained during autoregulation.

Drugs that eliminate smooth-muscle tone have been used in support of the myogenic theory. However, aside from the fact that autoregulation may be achieved in their presence, they produce effects that would upset the tissue-pressure-arterial-pressure relationships; namely, the afferent vessel tone is decreased so greatly that even at low arterial pressures the kidney is grossly swollen and has a greatly increased tissue pressure. This finding is similar to the results obtained with saline infusion. Such drugs may also unleash the full force of renal-artery pressure on the capillaries so that glomerular vessels are ruptured, and the preparation would thus become unfit for experimental use.

Summary

A series of eighteen experiments have been carried out on the heart-lung perfused dog kidney, and the results have defined the role of the intrarenal veins in the autoregulation phenomenon. It was found that there are a variety of intrarenal venous pressures which differ greatly according to (a) anatomical location and (b) the prevailing renal-artery pressure.

Findings have pointed out the importance of correct techniques in establishing the changes occurring in the intrarenal venous flows.
MECHANISM OF AUTOREGULATION

segment in response to an increase in renal artery pressure.

An increase in ureteral pressure results in a significant decrease in renal blood flow and an increase in overall renal vascular resistance, which further supports the role of extravascular pressure increases in renal-flow regulation.

The findings of the present study corroborate previous reports from this laboratory indicating that autoregulation is primarily accounted for on the basis of changes in renal extravascular pressure. Evidence has been provided for the absence of the "myogenic reflex" as a causal factor in autoregulation.

Acknowledgment

The author wishes to express appreciation for technical assistance from Lorentz E. Wittmers, Margaret M. Jordan, and Susan O. Doty.

References

Role of Intrarenal Venous Pressure in the Regulation of Renal Vascular Resistance

LERNER B. HINSHAW and DAVID M. WORTHEN

Circ Res. 1961;9:1156-1163
doi: 10.1161/01.RES.9.6.1156

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1961 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/9/6/1156

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/