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J Clin Invest. 1951;**30**(10):1143-1155. <https://doi.org/10.1172/JCI102534>.

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EVALUATION OF RENAL RESISTANCES, WITH SPECIAL REFERENCE TO CHANGES IN ESSENTIAL HYPERTENSION¹

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(Submitted for publication December 13, 1950; accepted August 6, 1951)

We have elsewhere (1) treated the theoretic aspects of renal hemodynamics at some length, and there presented methods for the evaluation of the physical characteristics of the renal vascular tree. Unfortunately the application of these methods requires precise knowledge of certain variables not available at the present time. It is, however, possible by means of warrantable, simplifying assumptions to effect such simplification in the analytic approach as to make possible the calculation of the major renal resistances from clinically available data. This paper comprises a statement of the necessary assumptions, the equations based thereon, and the calculation of renal resistances in the normal human kidney and in subjects with hypertensive disease.

For practical computation the renal vascular tree can be divided into five functional segments:

- A = Afferent vessels
- B = Glomerular capillaries
- C = Efferent arterioles
- D = Peritubular capillaries
- E = Venules and veins

If the conditions in the intermediate segments B and D can be specified, the characteristics of the other three vascular segments A, C and E, can be approximately evaluated.

Glomerular and peritubular capillaries. Collating the available data on the nature of the fluid flow in capillaries (2), the relative viscosity of the blood for specified plasma protein concentration (3), and hematocrit (4, 5), the dimensions and number of the glomerular capillaries (6), and the blood flow through the glomerular capillary bed (7), it may be deduced that the glomerular capillaries contribute some 1.8 to 9 per cent of the total renal resistance; i.e., the drop in pressure along the glomerular capillaries is of the order of 1.4 to 7 mm. Hg, a value negligibly small as compared to the drop in pressure across the kidney as a whole (some 80 mm. Hg in normal subjects). This conclusion is supported by the fact that in different species the drop of pressure between the arteriolar and venous end

of the capillaries of the systemic circulation ranges from 3 to 20 mm. Hg (8).

As compared with the glomerular capillaries, the peritubular capillaries probably afford an equal or larger cross-sectional area through which the blood moves at a relatively low velocity, and with even a smaller decrement in pressure than in the glomeruli. In the absence of precise information, it may be assumed that the contribution of both the glomerular and peritubular capillary plexus to the total renal resistance is so small that it can be neglected in practical computations.

The elementary mathematical treatment which follows, however, is such that part of the actual resistance of the glomerular capillaries is subsumed in the calculated value of R_A and part in R_E , while part of the actual resistance of the peritubular capillaries is subsumed in R_E and part in R_V . The net effect, therefore, is to introduce a slight, unavoidable but probably negligible error in each of these terms.

For the calculation of the resistances represented by A, C and E, it is required that we know the flow across and decrement in pressure along each segment. The four pairs of values the members of which are to be compared are:

$$(1) R = \frac{P_m - P_v}{Q} \times 1328 = R_A + R'_E + R_V$$

$$(2) R_A = \frac{P_m - P_g}{Q} \times 1328$$

$$(3) R_E = \frac{P_g - P_t}{Q - q} \times 1328$$

$$(4) R_V = \frac{P_t - P_v}{Q} \times 1328$$

Q = afferent renal blood flow

q = filtration rate

both in cc./sec. and corrected to 1.73
sq. m. body surface area.

P_m = mean aortic pressure

P_g = mean glomerular pressure

P_t = mean peritubular capillary pressure

P_v = renal venous pressure

all pressures in mm. Hg

R = total renal resistance

R_A = afferent resistance

R_E = true efferent resistance

¹ Aided by grants from the Knapp Foundation and the Commonwealth Fund.

R'_E = net efferent resistance (to be defined later)

R_V = venular resistance
all resistances in dynes. sec. cm.⁻⁵

Correction of Q and q to standard body surface area must be made before incorporation into the equations because (a) the calculated resistances will thus be automatically corrected for body size as they should be; (b) the gross glomerular permeability coefficient $\bar{\lambda}$, as it appears in equation 5, is based upon a filtration rate already corrected for body surface area.

The factor 1328 is obtained by multiplying the weight of 0.1 cc. Hg at 20° C. (sp. gr. 13.546) by the acceleration of gravity (980.6 cm. sec.⁻²), transforming the pressure into absolute units or baryes (dynes. cm.⁻²) which, when divided by flow (cm.³/sec.), gives dynes. sec. cm.⁻⁵.

Basic premises

I. In speaking of "resistances" as calculated above, it must be recognized, first, that the relation between fluid flow and decrement in pressure in any vascular segment is not a linear one (2, 9-11), and second, that blood viscosity (2, 4, 12) and the force (the parameter, π) of permanent contraction of the smooth muscular fibers of the vascular wall² (2, 13-17) complicate the simple concept of "resistance" as a ratio of the decrement in pressure along a vascular segment to the flow. That is, this ratio does not constitute a resistance in the strict sense of Poiseuille's law or Ohm's law; neither does it constitute a conductance in the sense in which this word has

² The parameter, π , which has the dimensions of a pressure, has been identified by the writer with the active force of permanent semi-contraction of the smooth muscular fibers of the vascular walls. Together with the internal viscous resistivity of the arterial walls, the parameter π plays a most important role in the dynamic cubic expansion of the arterial reservoir (2). It also constitutes the preponderant factor determining the changes in frictional resistance to blood flow in the small vessels, the caliber of which is essentially defined by the value of this parameter (13-17). With this last connotation the existence of the parameter π has been subsequently recognized by Aperia (18) who, with the designation of "virtual static pressure" which we originally used, has made wide use of it in his hemodynamic studies. The significance of this parameter has been recently stressed again (19). A first attempt has been made to introduce this parameter in renal hemodynamics (1), but further experimental information is needed before such a concept can be used in clinical research (20).

been used by the writer (2, 13-16). But in identifying the above ratios as "resistances," we are following widely accepted hemodynamic usage. The chief consequence of this approximation is that "resistance" as here calculated will not vary strictly as the inverse of the fourth power of vessel diameter, as in the simple statement of Poiseuille's law, though changes in the resistance thus calculated will always represent changes in vascular diameter.

II. The following treatment neglects the loss of fluid from the blood as urine, which is not significant except at very large urine flows, and loss of fluid as lymph, the magnitude of which is small but unknown.

III. It is assumed that glomerular plasma flow and peritubular plasma flow represent an identical stream from which glomerular clearance is effected first, followed by tubular clearance and tubular reabsorption.

IV. It is assumed that the glomerular filtrate and the renal interstitial fluid are protein-free.

V. It is assumed that the specific permeability coefficient of the glomerular capillaries is constant in all subjects without glomerular disease, and excluding the limiting conditions discussed below.

VI. It is assumed that glomerular surface area is proportional to body surface area.

Calculation of total renal resistance, R

P_m , P_v and Q are clinically determinable, and therefore equation 1 may be solved directly.

P_m may be measured directly from the brachial or femoral artery, or estimated as $P_d + k(P_s - P_d)$, where P_s and P_d are systolic and diastolic auscultatory determinations and k is a factor³

³ An approximate value of k is given by the formula

$$k = 0.77\gamma + \rho(1 - \gamma)$$

where γ is the ratio of the duration of the systolic ejection phase to the entire duration of the cardiac cycle and ρ is the fraction of the pulse pressure corresponding to the mean value of the amplitude during diastole. Expressed in terms of the pulse rate, N , γ and ρ have the values

$$\gamma = \frac{2.3\sqrt{N}}{60}$$

and

$$\rho = \frac{12(3\gamma + 1)}{100}$$

When N is between 60 and 80, the value of k varies between about 0.390 and 0.45, in agreement with figures given in the literature. These equations are not valid in aortic insufficiency, pulsus alternans, and auricular fibrillation.

averaging 0.44 (21), or by other indirect means (2, 22-28).

P_v may be measured by catheterization of the renal vein, or taken as equal to femoral venous pressure. Where the peripheral venous pressure is not increased, P_v may be taken as 10 mm. Hg on the basis of average normal values. Where the venous pressure is greatly elevated, as in chronic congestive cardiac failure, P_v may be taken as equal to the peripheral venous pressure (29, 30).

Q is the effective renal blood flow as measured by the PAH or diodrast clearance without reference to the extraction ratio.

Calculation of afferent arteriolar resistance, R_A

This calculation involves P_m (*vide supra*) and the mean glomerular pressure, P_g ; the latter cannot be measured directly and must therefore be computed. The method of computation which follows is based on the accepted principle that the rate of glomerular filtration is proportional to the difference between the total mean glomerular pressure, P_g , and the sum of the mean oncotic pressure (h) and intracapsular (= interstitial) pressure (H). In the Starling-Cushny hypothesis of glomerular filtration, the glomerular membranes may be conceived to be a uniform filter possessing a fixed permeability to water which is the same in all normal subjects and which can be designated by $\bar{\lambda}$, a gross permeability coefficient corrected for body surface area. Hence

$$(5) \quad q = \bar{\lambda}(P_g - h - H)$$

Equation 5 is derived as follows: if q' is the filtration rate uncorrected for surface area, and λ the gross permeability coefficient in any individual,

$$(6) \quad q' = \lambda(P_g - h - H)$$

but,

$$(7) \quad \lambda = \epsilon S_g$$

where ϵ is the specific glomerular permeability coefficient (cc./sec. per unit glomerular surface area per unit effective glomerular pressure) and S_g is the total glomerular surface area. Where renal function is corrected to standard body surface area, we may designate these quantities by $\bar{\lambda}$ and \bar{S}_g , so that

$$(8) \quad \bar{\lambda} = \epsilon \bar{S}_g$$

Dividing (7) by (8),

$$(9) \quad \lambda = \frac{S_g \bar{\lambda}}{\bar{S}_g}$$

Under premise VI, glomerular surface area is taken as proportional to body surface area, S , and consequently

$$(10) \quad \lambda = \frac{S \bar{\lambda}}{\bar{S}}$$

Substituting 10 in 6,

$$(11) \quad q' = \bar{\lambda} \frac{S}{\bar{S}} (P_g - h - H)$$

Since by definition $q = q' \frac{\bar{S}}{S}$

$$(5) \quad q = \bar{\lambda} (P_g - h - H)$$

In obtaining the normal value of $\bar{\lambda}$, we must assign a value to the mean glomerular pressure, P_g , applicable to the statistical average normal subject. Winton's (31) indirect estimates in the dog indicate that the glomerular pressure is about two-thirds of the mean aortic pressure; taking the latter as 90 mm. Hg in normal subjects under standard conditions, we assign a value to P_g of 60 mm. Hg.⁴ By taking q as 2.167 cc./sec. (130 cc./min.) (32), and h and H as 25 and 10 mm. Hg on the basis of average normal values, $\bar{\lambda} = 0.0867$.

Rearranging equation 5,

$$(12) \quad P_g = h + H + \frac{q}{\bar{\lambda}}$$

Observations on the filtration rate, pelvic and interstitial pressures in dogs indicate that so long as the urine flow does not exceed 10 per cent of the filtration rate, the pressure in Bowman's capsule must be practically identical with the interstitial pressure (20). Consequently we utilize interstitial pressure, H , in equation 12 as a substitution for intracapsular pressure.

We have shown elsewhere (1) that the conditions determining interstitial pressure are such that, for wide variations in all renal resistances,

⁴ The selection of this value in order to define the properties of the normal glomerular membranes is arbitrary and might be designated as an additional premise. Actually, the value of P_g within the range 55 to 65 mm. Hg assumed in calculating $\bar{\lambda}$ has only a moderate influence upon the calculated value of R_A , R_g and R'_g , and no influence upon R_v .

this pressure is predominantly dependent on renal venous pressure, P_v .

The interstitial pressure, H , surrounding the renal venous network is properly defined by the relation

$$(13) \quad H = \frac{2K + aP_v + aK + a\sqrt{(P_v - K)^2 + \pi^2(1 + a)}}{2(a + 1)}$$

with

$$(14) \quad K = (P_m - h_o) - \frac{a}{2} (h_o + \sqrt{h_o^2 + \pi^2})$$

where h_o is the minimum oncotic pressure, K is a lower limiting pressure mentioned below, and a is a coefficient given by the product of the resistance from the aorta to the peritubular capillary network multiplied by the maximum conductance of the venous system (20). The symbol π , which has the dimensions of a pressure, is a parameter depending on the thickness of the vascular walls. When the latter is small, π is also small and the interstitial pressure varies as a function of the venous pressure as indicated above.

The renal interstitial pressure is also approximately defined (1) by the formula

$$(15) \quad H = \frac{R_v P_m + (R_A + R'_E) P_v}{R_A + R'_E + R_v} - h_o$$

in which each symbol is defined in the text. When the venular resistance R_v is considered as being passively influenced by the difference between the intravascular blood pressure and the extravascular pressure, H , the statement made in the text continues to hold within certain limits.

The above equations, however, contain renal characteristics for which values are not directly ascertainable, and consequently we must at present use the approximation method of relating H to P_v .

In theory, it may be expected that interstitial pressure will have a minimal value which is independent of P_v when the latter is below a limiting value, K , but to increase with and approach P_v where the latter is above this limit. This relationship has been confirmed experimentally (33, 34) in dogs and other mammals, the data showing that H has a value of about 10 mm. Hg so long as P_v is normal, and approaches P_v rapidly as the latter is increased.

Hence H is taken as 10 mm. Hg for normal renal venous pressures and as equal to the renal venous pressure when the latter is greater than 10 mm. Hg.

The oncotic pressure, h , can be calculated from the mean plasma protein concentration, C_m , in the glomerular capillaries,⁶ which in turn can be calculated from C_A , the con-

centration in the afferent plasma (in gm./100 cc.), the renal plasma flow, Q' , and the filtration rate, q , or alternatively from the filtration fraction, $F (= q/Q')$:

$$(16) \quad C_m = C_A \frac{Q'}{q} \ln \frac{Q'}{Q' - q} = \frac{C_A}{F} \ln \left(\frac{1}{1 - F} \right)$$

The variation of plasma flow $y(x)$ along the abscissa x in the glomerular capillaries is a complex one (1), but can be simplified to the practically linear relation

$$(17) \quad y(x) = Q' - q \frac{x}{L}$$

in which L is the length of the glomerular capillaries. If $C(x)$ is the protein concentration at any point, and C_o the initial concentration, one necessarily has everywhere

$$(18) \quad C(x)y(x) = C_o Q'$$

and, therefore,

$$(19) \quad C_m = \frac{1}{L} \int_0^L \frac{C_o Q'}{y(x)} dx = \frac{C_o Q'}{L} \int_0^L \frac{dx}{Q' - q \frac{x}{L}}$$

By performing the quadrature indicated here, one obtains equation 16. Alternatively one may take the arithmetic mean between C_A and C_E , the latter being the efferent protein concentration as measured by

$$(20) \quad C_E = C_A \frac{Q'}{Q' - q} = \frac{C_A}{1 - F}$$

and one obtains:

$$(21) \quad C_m = C_A \frac{Q' - q/2}{Q' - q} = C_A \frac{1 - F/2}{1 - F}$$

Equations 16 and 21 give the same result for small values of the ratio q/Q' , as shown by expanding in a power series the logarithmic term in 16 and the denominator in 21, neglecting all the terms of higher order than the first.

To relate C_m to oncotic pressure, we have used the empirical relationship

$$(22) \quad h = \alpha(C_m - \beta)$$

where α and β are numerical constants, the first having the dimensions of a pressure. From available data (35-39), when C_m lies between 5 and 8, α has a value of 5 mm. Hg and β has a value of 2. When C_m lies between 8 and 11, α has a value of 7.75 mm. Hg and β has a value of 4. The relationship is applicable, however, only if the albumin/total protein ratio is about 0.60 \pm 0.04.⁶

hemodynamics, are scarcely worth the elaboration. Our method of estimating h , as well as the method of estimating H , introduce slight errors in R_v , but are without significant effect on R_A and R_E .

⁶ The oncotic pressure can be related to plasma protein concentration and albumin total protein ratio by a more elaborate and precise formulation (20), but this need not be attempted here. The approximate relations given above are derived empirically but they can be justified by

⁶ It is obvious that the effective mean oncotic pressure in the peritubular capillaries will be slightly lower than in the glomeruli. To correct for this factor, however, one has to introduce involved calculations which, in view of the approximate nature of all equations pertaining to renal

After calculation of P_g by determination of h and H in equation 12, substitution in equation 2 yields R_A .

True efferent arteriolar resistance, R_E

It must be noted that a quantity, q , of fluid is shunted around the efferent arterioles by filtration and tubular reabsorption of water. We must therefore distinguish between the true efferent resistance, R_E , were this shunting absent, and the net efferent resistance, R'_E (*vide infra*), as calculated with due allowance for the shunt.

The calculation of R_E requires knowledge of the mean glomerular pressure, P_g , which is obtained as described above, and P_t , the mean pressure in the peritubular capillaries, which again must be estimated indirectly. In approaching the calculation of P_t , it may be noted that the permeability coefficient, λ' , of the peritubular capillary bed must be extremely large as compared to that of the glomerular capillaries, $\bar{\lambda}$. If the ratio $\lambda'/\bar{\lambda}$ were near unity, the blood pressure at the midpoint of the peritubular capillaries would have to approximate the value of the renal venous pressure, as can be shown by writing two equations, one, 23, for filtration, q , and one, 24, for reabsorption, \bar{q} :

$$(23) \quad q = \bar{\lambda}(P_g - H - h)$$

$$(24) \quad \bar{q} = \lambda'(H + h - P_t)$$

If we assumed that $\lambda' = \bar{\lambda}$, and writing $q = \bar{q}$, it would follow that

$$(25) \quad P_t = 2(h + H) - P_g$$

Substituting 60 for P_g and 35 for $H + h$, P_t would equal 10 mm. Hg, a value no greater than the known renal venous pressure. This condition could exist only if the resistance to flow in the renal venules and small veins were practically zero, whereas it is well demonstrated (8) that an appreciable decrement in pressure occurs distal to the venous side of the capillary network; assuming that the renal venous system does not differ from the systemic venous system, it follows that P_t must be assigned a value greater than P_v by a difference amounting to the fall in pressure across the venular resistance R_v , which, by equation 4,

a formal expansion in Taylor's series of the theoretical expression around selected values of protein concentration and albumin/total protein ratio.

is $R_v Q$. Consequently, $\lambda'/\bar{\lambda}$ must be greater than 1.

Approaching the question from another point of view, the volume of blood contained in the kidney is relatively large (we estimate this volume to be of the order of 15 to 30 per cent of the total kidney volume) and there is therefore no reason to suppose that the total capillary surface area per unit of blood is any less than in the systemic capillaries. It has been estimated that in the horse, dog and frog, 1 cc. of systemic blood is exposed to a capillary surface area of 7,300, 5,600 and 2,700 sq. cm., respectively (40, 8). Translating the above figures directly, and assuming a weight of 150 gm. per kidney, the total capillary surface area of the two kidneys would be of the order of 225,000 to 450,000 sq. cm. The surface area of the glomerular capillaries in man is variously estimated to be 15,600 (6, 40) and 7,600 sq. cm. (41). If the specific permeability coefficients (per unit surface area) were the same for both networks, the ratio $\lambda'/\bar{\lambda}$ would be of the order of 15 or 60 to 1. The pressure required to effect the separation of the glomerular filtrate is scarcely more than $(P_g - h - H)$ or 25 mm. Hg; to reabsorb this same quantity of fluid through a capillary plexus 15 to 60 times as large would require proportionately less pressure, or about 0.4 to 2 mm. Hg. Consequently P_t may be taken as no more than 2 mm. Hg below $(h + H)$ and the difference may be less.

From equation 24, writing $\bar{q} = q$ and neglecting the urine flow,

$$(26) \quad P_t = h + H - \frac{q}{\lambda'}$$

If, as argued above, λ' is many times greater than $\bar{\lambda}$, the term q/λ' becomes small, as compared to the actual values of $H + h$, and equation 26 approaches the equality

$$(27) \quad P_t \approx h + H$$

By eliminating $h + H$ between equations 23 and 26, one has

$$(28) \quad q = \frac{\bar{\lambda}\lambda'}{\bar{\lambda} + \lambda'}(P_g - P_t)$$

where $\frac{\bar{\lambda}\lambda'}{\bar{\lambda} + \lambda'}$ is equal to the compound total permeability of glomerular and peritubular

capillaries. Since $\lambda' \gg \bar{\lambda}$,

$$(29) \quad \frac{\bar{\lambda}\lambda'}{\bar{\lambda} + \lambda'} \approx \bar{\lambda}$$

and 28 becomes

$$(30) \quad q \approx \bar{\lambda}(P_g - P_t)$$

From 3 and 30 one obtains

$$(31) \quad R_E = \frac{q}{\bar{\lambda}(Q - q)} \times 1328$$

Net efferent arteriolar resistance, R'_E

In some instances it may be desirable to calculate the true efferent resistance as a distinct feature of renal function. It will be noted, however, that the glomerular filtrate which is reabsorbed by the peritubular capillaries contributes to the total renal resistance and must somehow be subsumed in equation 1. It could appear as an independent term but it seems preferable to subsume it in the efferent resistance, and for practical purposes to calculate the net or compound parallel resistance presented by the true efferent resistance and the resistance presented by filtration and reabsorption.

This net resistance, R'_E , is given by the total flow, Q , and the decrement in pressure between the glomerular and peritubular capillaries,

$$(32) \quad R'_E = \frac{P_g - P_t}{Q} \times 1328 = R_E \frac{Q - q}{Q}$$

Venular resistance, R_V

Substituting equation 27 in equation 4,

$$(33) \quad R_V = \frac{H + h - P_v}{Q} \times 1328$$

Renal shunts and uncleared blood

In the foregoing analysis we have treated the problem as though the clearance method directly gave the total renal blood flow, without reference to the extraction ratio, E_{PAH} . However, only some 92 per cent of the renal arterial blood is presented to the renal parenchyma for clearance. The other 8 per cent is presumably by-passed through perirenal fat, the renal capsule, the calyces, pelvis and other non-excretory tissue (31). Conceiving this uncleared blood as comprising an integrated "uncleared shunt" around the active renal parenchyma, the flow of blood through this shunt is

$$(34) \quad \frac{Q(1 - E_{PAH})}{E_{PAH}}$$

where E_{PAH} (or E) is the renal plasma extraction ratio of PAH. The resistance, R_s , of this shunt is

$$(35) \quad R_s = \frac{(P_m - P_v)E}{Q(1 - E)} \times 1328$$

The resistance corresponding to the effective renal blood flow is that defined in equation 1 as R . R and R_s are in parallel, and their combination from 1 and 35 gives the resistance, R_w , of the whole kidney (cleared and uncleared blood), which is obviously smaller than either R or R_s :

$$(36) \quad R_w = \frac{RR_s}{R + R_s} = \frac{E(P_m - P_v)}{Q} \times 1328$$

Locus of pressure equilibrium

At some point, a , along the efferent arteriole the value of the blood pressure necessarily comes to equal the sum of the maximal oncotic pressure h' and the interstitial pressure, H . This point may be represented as a fraction, a , of the efferent arteriolar resistance encountered between the end of the glomerulus, in the sense where filtration ceases, and the beginning of the peritubular capillaries, in the sense where capillary reabsorption begins, this entire length representing the efferent arteriolar resistance, R_E . The maximal oncotic pressure, h' , is given by

$$(37) \quad h' = \alpha(C_E - \beta)$$

where α and β (*vide supra*) lie within the limits specified in connection with equation 22 and C_E is defined by equation 20.

That portion of the resistance encountered between the glomerulus and the locus of pressure equilibrium is given by the relation

$$(38) \quad aR_E = \frac{P_g - (h' + H)}{Q - q} \times 1328$$

which divided by equation 3 yields

$$(39) \quad a = \frac{P_g - (h' + H)}{(P_g - P_t)}$$

In terms of the characteristics of the renal vascular tree and the external forces applied to it, the fraction a is defined by the equation

$$(40) \quad a = \left\{ 1 - \frac{R(h_0 + \alpha\beta)}{2(P_m - P_v)[1328(1 - \phi) - \bar{\lambda}R'_E]} \right\}$$

where α and β are the constants defined in equation 22, ϕ is the hematocrit taken as a decimal. This relation holds within the limits imposed by the restrictive conditions specified above and can be drawn from the equations given in the text.

The resistance, R^A , between the aorta and the locus of pressure equilibrium⁷ is

$$(41) \quad R^A = \frac{P_m - (h' + H)}{Q} \times 1328 \\ = R_A + \frac{aR_E \times 1328}{\bar{\lambda}R_E + 1328} = R_A + aR'_E$$

⁷ These two relations (equations 41 and 42) have been reported previously (42). However, the notations have been changed ($b = aR_E$) and the permeability coefficient of the peritubular capillary network has been considered

while the resistance, R_E^E , from this equilibrium point to the vena cava at the level of the kidney is

$$(42) \quad R_E^E = \frac{(h' + H) - P_v}{Q} \times 1328$$

$$= R_v + \frac{(1 - a)R_E \times 1328}{\bar{\lambda}R_E + 1328} = R_v + (1 - a)R'_E$$

Practical applications and limitations

In one important respect the approach outlined above is different from that presented by Smith and associates (43), who assumed that filtration equilibrium is reached in the glomerulus. For such to be the case, most of the renal vascular resistance would have to be concentrated in the glomerular capillaries (which is equivalent to assigning practically zero resistance to the afferent, efferent and venular segments), and the gross permeability coefficient of the glomeruli would have to be as great as or greater than that of the peritubular capillaries. If such were the case, the filtration rate and the interstitial pressure would vary over wide ranges with variations in renal blood flow. The postulate that filtration equilibrium is reached in the glomerulus contradicts many theoretical and practical considerations (1) and is untenable. Lampert (44, 45) has used this assumption, and because the premise is untenable, the equations based thereon are also invalid. Other assumptions enter into his equations which are un-

as having a value many times greater than that of the glomerular capillaries.

satisfactory, but space does not permit us to discuss them here.

In practical computations, q , Q' and Q are corrected to standard surface area, C_m is calculated by equation 16 and h is calculated from equation 22. Selecting the appropriate value of H , P_g is calculated by equation 12. P_t is calculated by equation 27. These values are then introduced in equations 2, 3 and 4. R'_E is then calculated from equation 32.

The above equations are subject to the following limitations:

a) Equations 1 to 4 by definition are applicable to clearance data where E_{PAH} (or E_D) can be assumed to be high (90 per cent or above), so that the contribution of un-cleared blood to renal resistance can be neglected, and where E_{PAH} (or E_D) is known, the contribution of un-cleared blood can be treated by equations 35 and 36. But where E_{PAH} (or E_D) has been reduced by disease the equations by definition are no longer applicable. The question of applicability in the presence of possible renal impairment must be considered on its own merits, with reference to every assumption made, as in the following discussion of renal resistances in patients with essential hypertension.

b) Equations 12 and 27 (and hence equations 2 and 3) should be applied with caution to patients with glomerular disease (acute and chronic glomerulonephritis, glomerulocapillary sclerosis, nephrosis, amyloidosis, etc.) because they involve the assumption that the gross glomerular permeability coefficient has the calculated and idealized normal value, $\bar{\lambda}$. For the same reason, the applicability of

TABLE I

Renal vascular resistances in normal subjects

P_m indicates the mean arterial blood pressure, $60q$, $60Q'$, and $60Q$, the filtration rate, effective renal plasma flow and effective renal blood flow, respectively, per 1.73 sq. m. body surface area. Resistances are given in c.g.s. units (dynes sec. $cm.^{-5}$). The term a is defined in the text.

No.	Subject	Age	P_m	$60q$	$60Q'$	F	$60Q$	R	R_A	R_E	R_v	a
		Years	mm. Hg	cc./min.	cc./min.	per cent	cc./min.	Dynes sec. $cm.^{-5}$				
1	E. C.	51	90	143	684	21	1242	5126	1434	2085	1779	0.87
2	J. W.	51	93	170	669	25	1218	5432	1022	2696	2111	0.83
3	D. S.	50	80	119	364	33	670	9800	2523	4369	3864	0.68
4	E. D.	27	83	116	666	17	1254	4635	1912	1673	1182	0.88
5	J. B.	50	102	122	548	22	828	8752	3174	2895	3134	0.43
6	P. Q.	36	84	96	827	16	1362	4329	1368	1262	1726	0.86
7	H. K.	23	110	146	624	23	1104	7211	2430	2523	2656	0.80
8	S. M.	31	88	128	612	21	1134	6812	890	2098	2722	0.67
9	A. M.	42	84	106	648	16	1200	4914	1195	1607	2243	0.78
10	F. T.	40	90	90	429	21	762	8366	3240	2231	3134	0.80
11	S. C.	47	105	147	661	22	1116	6786	2456	2523	2138	0.84
12	E. K.	38	100	123	654	19	1086	6640	2576	2138	2138	0.84
13	T. K.	29	88	147	768	19	1320	4714	1102	2085	1766	0.87
14	R. W.	42	85	108	684	16	1092	5471	1766	1819	2058	0.86
15	J. S.	45	94	130	798	16	1242	5392	1872	1939	1779	0.90
16	J. W.	35	80	130	756	17	1374	4064	823	1740	1660	0.86
17	F. F.	31	95	146	520	28	906	7477	1992	3200	2802	0.78
18	E. O.	45	91	97	594	16	900	7171	2868	1992	2523	0.84
19	J. D.	62	98	123	587	20	906	6866	1992	2603	2603	0.82
20	A. M.	36	88	103	563	18	936	6640	2350	2058	2470	0.82
21	W. M.	33	96	122	529	23	978	7012	2961	2377	1965	0.82
22	O. D.	25	92	198	768	26	1410	4635	1938	1806	2390	0.90
Average			91	128	630	20	1098	6281	2005	2258	2240	0.81

TABLE II
Renal resistances in subjects with essential hypertension
Data as in Table I

No.	Subject	Age	P _m	60q	60Q'	F	60Q	R	R _A	R _E	R _V	a
		Years	mm. Hg	cc./min.	cc./min.	per cent	cc./min.	Dynes sec. cm. ⁻⁴				
1	A. W.	44	193	65	317	21	455	32005	24515	2788	5179	0.67
2	J. D.	45	162	84	297	28	513	23771	16733	2855	5117	0.41
3	T. V.	59	162	83	267	31	496	25099	16866	3360	5312	0.57
4	S. B.	36	158	86	382	23	744	15800	10737	2178	3240	0.71
5	M. R.	61	152	74	346	21	651	20186	13758	2536	4223	0.70
6	J. S.	71	150	74	315	23	501	22310	14688	2868	4834	0.59
7	C. M.	39	146	65	405	16	524	20717	14342	2364	4980	0.75
8	G. M.	50	145	83	459	18	768	13944	9203	2032	3001	0.78
9	M. B.	33	142	98	436	22	738	14210	8805	2536	3240	0.75
10	J. M.	51	142	98	391	25	714	14741	9150	2510	3400	0.72
11	D. T.	55	140	97	328	29	546	18326	11567	3572	3864	0.69
12	H. H.	49	135	100	758	13	1450	6866	4196	1235	1527	0.87
13	L. M.	52	125	106	529	20	846	10836	5976	2377	2776	0.80
14	R. S.	37	124	96	474	21	864	10518	4754	2390	2696	0.82
15	J. R.	47	124	122	459	26	800	11354	5570	3028	3240	0.74
16	I. L.	45	120	105	706	14	1018	8605	3997	1912	2191	0.91
Average			145	89	403	22	721	16790	10900	2520	3670	0.72

these equations to infants in whom the fetal glomerular membranes persist (32), and in senile individuals in whom many glomeruli may be canalized, is inappropriate.

c) For equation 22 to be valid, the systemic plasma concentration of total protein should not be below 5 nor above 8 gm./100 cc. and the albumin/total protein ratio should be between 0.55 and 0.65.

d) The renal blood flow, corrected for body surface area, should be above one-third (400 cc./min.) of its normal value (1200 cc./min.); otherwise the concept of resistance as a simple ratio between flow and pressure (equations 1 to 4 inclusive) will probably become grossly inaccurate.

e) It is improbable that equation 12 will be valid if the filtration rate is markedly reduced (<50 cc./min.), and under these conditions it is less likely that the renal interstitial pressure, H , can be equated with the intracapsular pressure.

f) The filtration fraction should not exceed 33 per cent of the renal plasma flow, because at higher values the approximation equation 27 becomes inaccurate.

g) Cases where the calculated values of P_g are above 75 or below 45 mm. Hg should be considered as of doubtful accuracy because great changes around the median value 60 mm. Hg would imply excessive expansion or contraction of the glomerular membranes and consequently changes in the specific glomerular permeability coefficient.

h) Caution must be used in interpreting the causation of changes in R_A , R_E or R_V . Active constriction of the efferent arterioles, for example, will by reduction of pressure distally elicit passive constriction in the venular system with an increase in R_V , while having converse passive effects upon the afferent arterioles and R_A . There is no way at the present time to distinguish passive from active changes in any of the vascular segments, and the effects of drugs, disease, etc. must be interpreted with this qualification.

Renal resistances in normal subjects under standard conditions

For the calculation of renal resistances in normal subjects under standard conditions we have used data reported by Bolomey and associates⁸ and unpublished data collected in this laboratory by Drs. Maxwell, Breed and Fishman. The resistances given in Table I are calculated from the data there recorded using $P_v = 10$ mm. Hg: where the plasma protein concentration was not available (about half of the cases), this value was assumed to be 7 gm./100 cc. The calculated resistances recorded in Table I require only one comment: the resistance of the venular system, R_V , is significantly large in respect to the total renal resistance, R , and in the average equals the resistance of either the efferent or afferent arterioles.

The value a , representing the fraction of the

TABLE III
Renal resistances calculated from the data of Corcoran, Taylor and Page (47) on subjects with essential hypertension

	P _m	60q	60Q	R	R _A	R _E	R _V
Highest	200	152	1459	30215	22284	3744	4878
Lowest	108	71	528	6786	3944	1622	1368
Average	150	99	848	18675	13930	2549	2536

* We are indebted to Dr. Lauson, and Drs. Corcoran, Taylor and Page for additional information not included in the published reports (46, 47).

effluent resistance R_E corresponding to the point at which pressure equilibrium is reached, needs no comment at this time, the data supplying a basis of reference in connection with shifts in this value during disturbances in the renal circulation.

Renal resistances in subjects with essential hypertension

The data on hypertensive subjects analyzed here comprise 11 subjects reported by Bolomey and co-workers (46) (Table II), five subjects on whom unreported data were available in this laboratory, and 35 subjects reported by Corcoran, Taylor and Page (47, 48) (Table III). Here again P_v was assumed to be 10 mm. Hg and the plasma protein concentration where not available was taken as 7 gm./100 cc.

It is known that in advanced stages of essential hypertension the extraction ratio of diodrast or PAH may be reduced (49-51) to such an extent that the clearance of these substances falls markedly below the total renal plasma flow. It is also known that the apparent filtration fraction may increase in some subjects to values ranging from 0.30 to 0.50, a circumstance which Goldring and associates (52) attributed to the formation of impotent nephrons in which, despite the persistence of glomerular filtration, tubular extraction is impaired. Whether the two phenomena are related has not been deter-

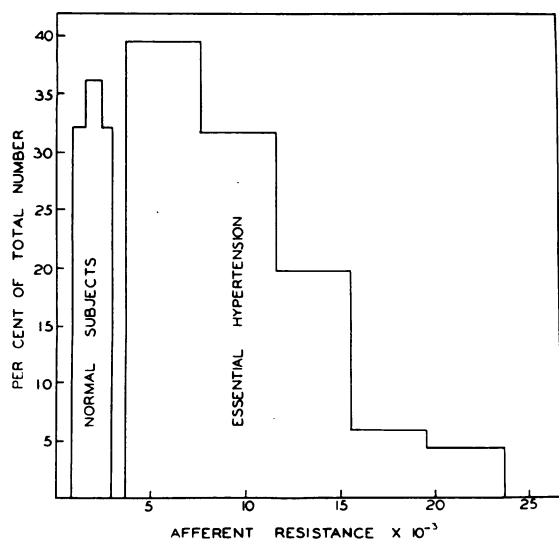


FIG. 1. DISTRIBUTION OF AFFERENT ARTERIOLAR RESISTANCE IN NORMAL AND HYPERTENSIVE SUBJECTS

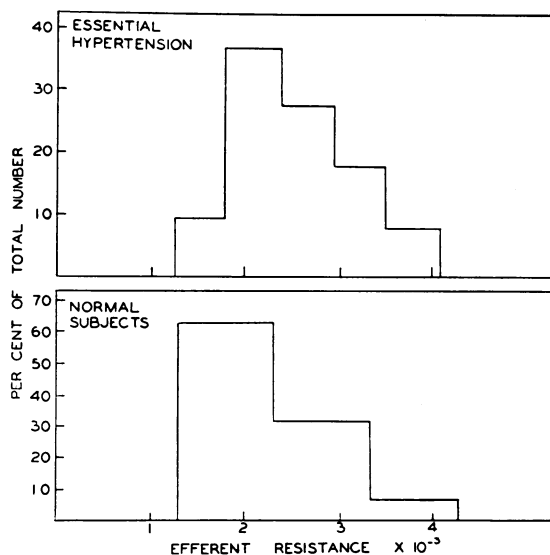


FIG. 2. DISTRIBUTION OF EFFERENT ARTERIOLAR RESISTANCE IN NORMAL AND HYPERTENSIVE SUBJECTS

mined, but it is highly probable that in any subject in which renal impairment has progressed to the point where the apparent filtration fraction is above the normal parameter (32) of $m + 2\sigma$, (c. 0.27), assumption III is inapplicable. Consequently we have selected for analysis only those subjects in whom the filtration fraction lies below 0.30. We have furthermore excluded subjects in whom the filtration rate is less than 65 cc./min., or the renal blood flow below 400 cc./min. None of the subjects showed evidence of cardiac failure or specific renal disease.

The results of our analysis of the two series are so similar that they will be considered together in the following discussion and in the figures.

The following points merit specific comment:

a) The frequency distribution of R_A among the hypertensive subjects is compared with the normal distribution in Figure 1. The lowest value of R_A among the hypertensive subjects exceeds the highest normal value.

b) Although R_E (and consequently R'_E)⁹ tends to be moderately increased, the mode lies below the upper normal limit in the frequency distribution curve (Figure 2). The data will not enable us to determine whether this increase

⁹ R_E rather than R'_E has been given in Tables I, II and III because the latter can be calculated directly as $R - (R_A + R_v)$.

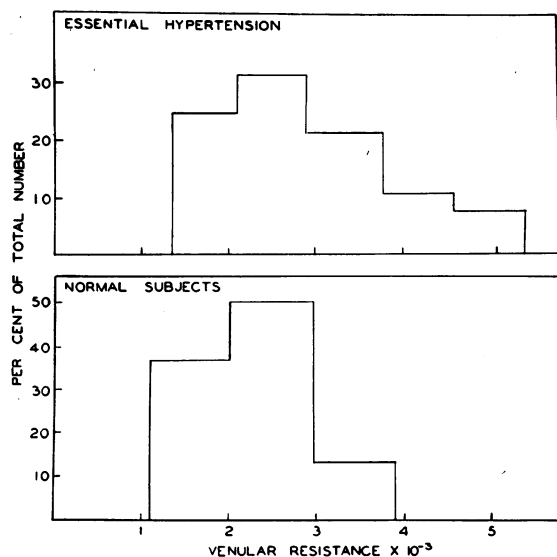


FIG. 3. DISTRIBUTION OF VENULAR RESISTANCE IN NORMAL AND HYPERTENSIVE SUBJECTS

is active or whether it is a passive consequence of the reduction in glomerular pressure.

c) Venular resistance is also elevated in the mean, but the mode still lies within the upper normal range (Figure 3).

d) Total resistance, R , is increased in nearly all hypertensive subjects, this increase being attributable predominantly to the increase in R_A (Figure 4).

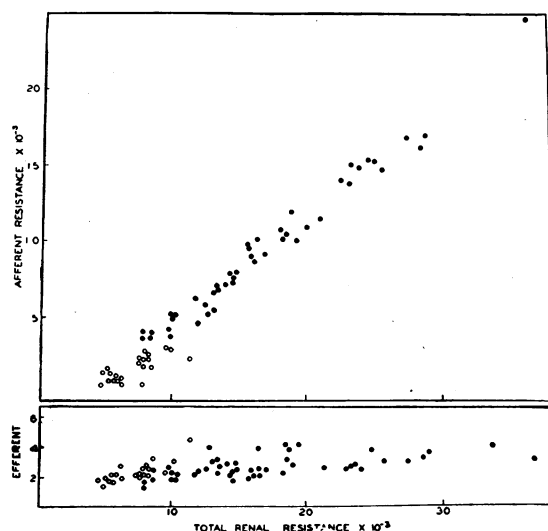


FIG. 4. VARIATIONS OF AFFERENT (ABOVE) AND EFFERENT (BELOW) ARTERIOLAR RESISTANCE WITH THE TOTAL RENAL RESISTANCE IN NORMAL (OPEN CIRCLES) AND HYPERTENSIVE (DOTS) SUBJECTS

e) One might anticipate that the increased afferent resistance would parallel the increase in systemic arteriolar resistance, in which case the renal blood flow and filtration rate would remain unchanged from normal in the face of increased arterial pressure. However, such is not the case; the renal resistance increases relatively more than the systemic resistance. To illustrate this point we note that in the majority of hypertensive subjects reported by Bolomey and associ-

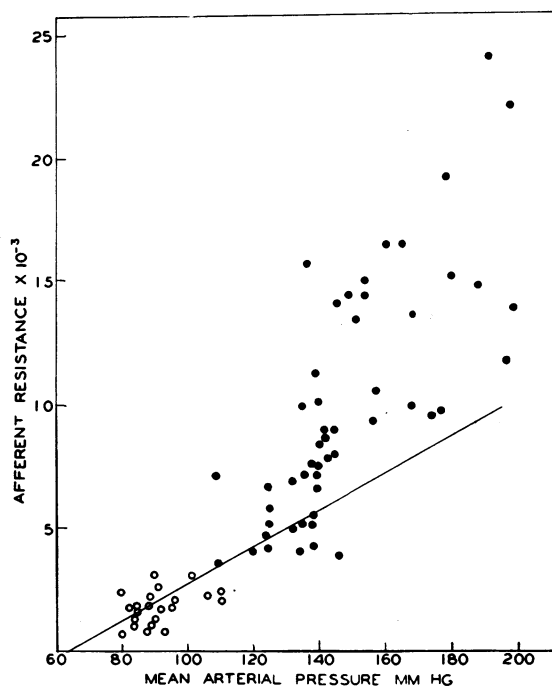


FIG. 5. AFFERENT ARTERIOLAR RESISTANCE IN RELATION TO MEAN ARTERIAL PRESSURE IN NORMAL (OPEN CIRCLES) AND HYPERTENSIVE (DOTS) SUBJECTS

The line indicates the changes in afferent resistance to be expected with increasing arterial pressure if renal blood flow and filtration rate retained the average values observed in the normal subjects represented by the open circles.

ates (our Table II), the cardiac output had the same modality and range as in their control subjects (our Table I). Therefore, the mean arterial pressure may be used as a rough index of the resistance in the systemic arteriolar bed. If in equation 2 we substitute the average normal values of Q (18.3 cc./sec.) as given in Table I and the average value of P_g as calculated from these data ($= 63.5$ mm. Hg), and solve for R_A as a function of P_m , we obtain the solid line in Figure 5. This line represents the values of R_A re-

quired at increasing values of P_m to yield a constant renal blood flow and filtration rate in the face of increasing P_m . It is clear that with increasing hypertension, there is a relatively greater increase in resistance in the afferent renal arterioles than in the systemic arterioles as a whole. These calculations give more exact expression to the well demonstrated fact that the renal blood flow tends to decrease below the normal value with advancing disease, despite the increase in blood pressure (31).

Our analysis indicates that the consistent and characteristic change in the renal circulation in essential hypertension is in afferent arteriolar resistance, which may be increased several fold: the increase in the efferent arteriolar and venular resistance, slight as it actually is, may be in part attributable to the passive decrease in caliber which results from the resulting decrease in glomerular and post-glomerular pressure.¹⁰

When Goldring and colleagues (52) concluded that essential hypertension was characterized by increased efferent arteriolar tone (R_E as here defined), they attempted no quantitative analysis of afferent arteriolar or venular tone, and they were led to their conclusion by inadequate analysis of hemodynamic factors, as cited earlier in this paper. Our present study forces us to accept that the increase in R_E as here calculated is at most a slight one; the outstanding change in renal hemodynamics is reflected in the increase in afferent resistance. Our analysis throws no light on whether this increase is anatomical or functional, but the demonstration by Goldring and associates (52) that the renal hyperemia induced in most hypertensive subjects by pyrogen is comparable in degree to that induced in normal subjects is evidence that the predominant factor is functional.

SUMMARY

1. Equations are developed for the calculation of the total renal resistance, R , the afferent arteriolar resistance, R_A , the pure efferent, R_E , and the net efferent arteriolar resistance R'_E (a term that includes the diversion of the glomeru-

lar filtrate around the efferent arteriole), and the venular resistance, R_V .

2. The calculations are based upon the clinically determinable variables of mean arterial blood pressure, the renal blood flow and plasma flow, the filtration rate, the protein concentration of the blood and the renal venous (or the femoral) pressure. Assumptions with respect to renal interstitial pressure and other matters pertinent to the validity of the working equations are stated in the text. Some of the limiting clinical conditions under which the working equations are applicable are defined.

3. Calculations are presented for the above resistances in 22 normal subjects who had been examined under standard conditions. A hitherto unrecorded datum is the relatively large magnitude of the renal venular resistance, which in the average equals the resistance of either the efferent or afferent arterioles.

4. Data on 51 subjects with essential hypertension reveal that the predominant change in the renal circulation in this disease is an increase in afferent arteriolar resistance. This increase is relatively greater than the increase in the resistance of the systemic arterioles.

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¹⁰ In view of the above results, the excessive increase in filtration fraction which is so generally characteristic of the disease in its advanced stages should be referred in considerable part to failure of tubular clearance (impotent nephrons) rather than to increased glomerular pressure.

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