Microvascular blood flow: evidence indicating a cubic dependence on arteriolar diameter

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MAYROVITZ, HARVEY N., AND JOHN ROY. *Microvascular blood flow: evidence indicating a cubic dependence on arteriolar diameter.* Am. J. Physiol. 245 (Heart Circ. Physiol. 14): H1031–H1038, 1983.—The primary objectives of this study were *1)* to determine the functional relationship between microvascular blood flow ($\dot{Q}$) and arteriolar internal diameter (D) and *2)* to determine whether this relationship conformed to a theoretical optimality prediction—that blood flow is proportional to the cube of the diameter ($\dot{Q} = kD^3$). Paired blood velocity and arteriolar diameter measurements in the cremaster muscle microvasculature of eight normotensive (WKY) and eight hypertensive (SHR) rats were made under control conditions and following maximal dilation of the microvasculature with topically applied adenosine. A total of 160 paired flow-diameter measurements were made in arteriolar vessels with diameters ranging from 6 to 108 μm. Analysis of this data showed that $\dot{Q}$ and D were functionally linked by $\dot{Q} = kD^m$ with $k = 417$ and $m = 3.01$ with D expressed in centimeters. Confidence intervals at the 99.9% level were 331–503 and 2.86–3.14 for k and m, respectively. A theoretical development based on the minimization of the energy cost of blood volume and arteriolar wall volume led to a theoretical estimate for the range of k to be 92–132 and a value for m to be 3. Predicted pressure gradients in single vessels of the cat mesentery and shear rates in the rat cremaster based on $\dot{Q} = kD^3$ compared well with measured data reported in the literature and that determined in the present study. On the basis of the direct and predictive evidence, it is concluded that the relationship $\dot{Q} = kD^3$ represents a general average property of the microvasculature.

microcirculation; optimality concepts; vascular optimality; hemodynamics; hypertension; spontaneously hypertensive rat; cremaster muscle microvasculature

THE WELL-KNOWN Poiseuille relationship states that, under appropriate hemodynamic conditions in isolated vessels, blood flow is proportional to the fourth power of the vessel's diameter. However, the practical applicability of this relationship to each vessel of the array comprising the microvasculature requires specific knowledge of the pressure gradient associated with each vessel segment. Such detailed information is virtually impossible to obtain experimentally. By virtue of the complex topography of the vascular network it is clear that not only will the blood flow in a vessel be dependent on its own diameter but also on the distribution of hemodynamic resistance throughout the microvascular bed. It is this overall resistance distribution that ultimately determines the pressure gradient for each vessel segment and thus provides the link between vessel diameter and the blood flow through it. Data from virtually all microvascular and macrovascular studies show that average arterial diameters progressively diminish as the capillaries are approached. This general observation is consistent with the teleological notion that a correspondence between the diameter of a vessel and the amount of tissue it supplies should be expected. However, no specific relationship linking blood flow and vessel diameter under in vivo conditions has yet been established.

In 1926 Murray (18) employed the principle of minimum work, which may have laid a theoretical foundation for significant insight into this problem. By simultaneously minimizing the energy-equivalent cost of blood flow ($\dot{Q}$) and blood volume he concluded that an optimal economy of circulation is realized if $\dot{Q}$ is everywhere proportional to the third power of the vessel's diameter ($\dot{Q} = kD^3$). Although this prediction has far reaching implications, no systematic test of its in vivo applicability has been reported. In spite of this, the theoretical result ($\dot{Q} = kD^3$) was subsequently used to calculate optimal arterial branching angles in terms of the diameters of the involved vessels (8, 19) and forms the basis for the commonly used cross-sectional area ratio (1:1.26) between parent and daughter vessels at arterial bifurcations (16, 17, 22, 29). It has been proposed (27) that the physical mechanism responsible for the development of such an optimal branching structure is total shear force minimization. The mathematical development on which this hypothesis is based included no assumption regarding $\dot{Q}$, but it was emphasized that experimental data on flow-diameter relationships were sadly lacking. This point was again emphasized (28), but the optimal flow-diameter concept ($\dot{Q} = kD^3$) was used to compare four optimality principles with regard to their branching angle-diameter predictions (30). Photographs of the retinal vasculature taken of one subject were used to assess the adequacy of these predicted results, which were, not surprisingly, inconclusive (31). Data derived from arterial casts (23) and postmortem angiography of human coronary arteries (7) tend to support the applicability of the predicted optimality relationship. However, because this data is based on purely anatomic considerations derived from tissues in the nonliving state, the fundamental issues remain unresolved.

The purpose of the work reported here was to determine if in vivo blood flow is in fact related to vessel diameter in the optimal manner originally put forward—is flow proportional to the cube of the vessel diameter?

A suitable test of this concept requires that at least three criteria be met: *1*) vessel inside diameter measurements must be made with an adequate degree of accuracy in view of the third-power dependence, *2*) $\dot{Q}$ must be determined in vivo simultaneously with the diameter measurements, *3*) measurements should be obtained under control conditions as well as under conditions of altered physiological and/or pathological states to test the generality of the principles. To address these issues, 160 paired simultaneous measurements of blood velocity and diameter obtained from the cremaster microvasculature of normotensive and hypertensive rats under control and maximally dilated conditions were used to assess the parameters and in vivo applicability of the relationship $\dot{Q} = kD^m$.

MATERIALS AND METHODS

Experimental preparation. Eight male Wistar Kyoto (WKY) and eight spontaneously hypertensive rats (SHR) of the Okamoto and Oaki (20) strain, F-34 generation, were used in this study. All rats were 7–8 wk old and weighed 106–120 g. Prior to having the cremaster muscle prepared for microscopic observation, each animal was anesthetized with a single dose of pentobarbital sodium (5.0 mg/100 g body wt ip). The animal was then placed on a heated mat, a tracheal cannula was inserted (3 cm length of PE-200 tubing), and the left carotid artery was isolated from the surrounding muscle. Actual cannulation of the carotid artery, for systemic blood pressure recording, was left until after the cremaster muscle was prepared.

The technique used to prepare the cremaster muscle for microscopic study is adapted from the method reported by Baez (2). Briefly, the cremaster muscle is separated from the scrotal sack by blunt dissection and kept moist by a constant flow of Krebs solution maintained at 34°C throughout the surgical procedure. The Krebs solution consists of (in mM) NaCl 113, dextrose 11.6, KCl 4.7, $MgSO_4 \cdot 7H_2O$ 1.2, KH_2PO_4 1.2, $CaCl_2 \cdot 2H_2O$ 2.6, and $NaHCO_3$ 25. The solution is bubbled with a gas mixture of 95% N_2-5% CO_2 to control the pH at 7.40. An incision is made on the caudal-ventral side of the muscle and continued to the level of the annulus inguinalis. Small bleeders are promptly tied off with 6-0 suture thread, which also serves as tether points for spreading the tissue. The major vessels running within the mesoepididymus are cauterized, and a cut is made rostrally along the interface between the mesoepididymus and the cremaster muscle up to the annulus inguinalis. The testis is then introduced into the abdominal cavity. The muscle is spread over a specially designed, optically clear heated pedestal, which is thermostatically controlled to maintain the tissue at 34 ± 0.1°C. The upper portion of the pedestal forms an open chamber that permits the muscle to be superfused at a rate of 2 ml/min. After completion of the muscle preparation, the left carotid artery is cannulated (18 cm length of PE-50 tubing) and connected to a BD two-way stopcock manifold to which an extra port is added to allow simultaneous blood pressure recording (Ailtech MS-20 semiconductor blood pressure gauge) and a constant infusion (0.00237 ml/min) of a heparinized (10 U/ml) anesthetic solution (Inactin 0.076 mg/min). The infusion maintains the animal at a constant level of anesthesia, keeps the blood pressure cannula patent at all times, and replaces lost fluid volume due to respiration, which occurs throughout the experiment. After these procedures the animal, already secured to a mounting board, is placed on the stage of a Leitz Ortholux trinocular microscope with a 150-W xenon light source. The muscle preparation is allowed to stabilize for 1 h before any measurements are made.

Measurements. Velocity measurements were made using the modified dual-slit method (25) with on-line cross correlation (24). The system dynamically analyzes the delay between upstream and downstream red cell photometric signals at a known distance apart to estimate center-line velocity. In the present study the two signals are obtained by placing two phototransistors in the optical path of a projected vessel image within a specially constructed housing incorporating a head amplifier. The sensor spacing (referred to the preparation) is 5 μm with a ×32 objective (n.a. 0.60) and 16 μm with a ×10 objective (n.a. 0.25) with an overall magnification of 640 and 200, respectively. The signals are preamplified, bandwidth limited to 2 kHz, and AC coupled before being fed into a tracking cross-correlation device (IPM). The velocity system is calibrated using a wheel rotating at a known speed placed in the visual path of the microscope setup. The output of the cross correlator is adjusted to provide an on-line display of the red cell velocity within the vessel under observation. The internal diameter of each vessel in which velocity is measured was determined with an eyepiece micrometer. In vitro calibration for diameter measurements is done using a stage micrometer having lines spaced at 10-μm intervals. By use of a micrometer field of 100 μm, a calibration factor for the eyepiece graticule is established as 1.8 μm/graticule line for the ×32 objective and 5.8 μm/graticule line for the ×10 objective. Repeated measurements of known distances between 90 and 10 μm have shown that the graticule can be estimated to the nearest quarter of a line thus indicating an absolute error of approximately ±0.45 and ±1.45 μm at ×32 and ×10, respectively. Little spontaneous change in vessel diameter was noted during in vivo measurements, which for each vessel order and procedure lasted about 4 min. In all cases the time-average diameter and velocity over this measurement period was used.

The arterial blood vessels of the cremaster muscle microvasculature were assigned to categories according to their branching order (Fig. 1). The major feeding artery (the cremasteric artery) is by convention designated first order. Succeeding branches are assigned consecutive order numbers from 2 through 5; the fifth-order vessels in this preparation directly supply capillaries. Consecutive velocity and diameter measurements were made on first- through fifth-order arterial vessels. To allow efficient hemodynamic comparisons in the two groups of animals, these measurements were made at strategic sites within a standardized arterial pathway. This pathway permits velocity and diameter measurements to be made on the first branch of each branching order as close as technically possible to the parent vessel. The only exception to this was in the first-order vessel in which velocity is measured slightly distal to the sec-

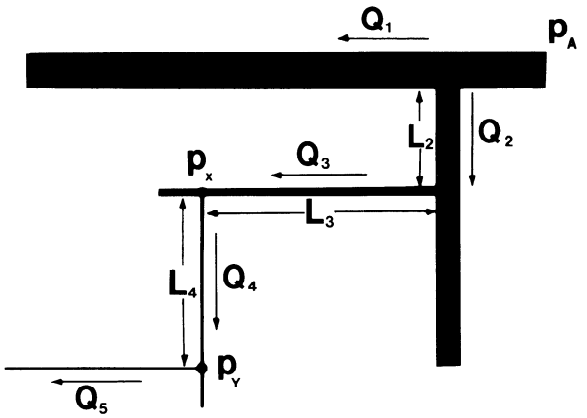

FIG. 1. Schematic representation of 5 vessel orders in which blood flow ($\dot{Q}$) was determined. In all cases these measurements were made on 1st branch of each consecutive branching order. Quantities p_x and p_y represent microvascular pressures; L_2 through L_4 represent vessel segment lengths, which are referred to in DISCUSSION.

ond-order branch, because the origin of the first-order vessel is out of the field of view.

The mean blood velocity (V_m) together with vessel internal diameter (D) were used to calculate the blood flow ($\dot{Q}$) from the formula $\dot{Q} = V_m (\pi D^2/4)$. This calculation assumes a cylindrical vessel shape. The measurements obtained from the cross correlator are center-line velocity (V_{cl}), and a correction factor is needed to convert to mean velocity. For microvessels greater than 17 μm in diameter the equation $V_m = V_{cl}/1.6$ is employed (3). Below a vessel diameter of 17 μm the radial velocity profile changes, and a correction factor of 1.3 may be more appropriate and was used (11). However, the effect of using both correction factors in this manner was compared with that of using a single correlation factor of 1.6 for all vessels and was shown to be inconsequential in the results obtained.

After control blood flow and diameter data were obtained, the muscle bed was dilated with a 1 mM topical dose of adenosine, which had no measurable effects on systemic blood pressure. Following this procedure, blood flow and diameter were again determined along the same arterial pathway.

Experimental data handling. The basic relationship tested was of the form $\dot{Q} = kD^m$. To evaluate k and m from the experimentally determined paired $\dot{Q}$ and D values, this equation was logarithmically transformed to $\ln(\dot{Q}) = \ln(k) + m\ln(D)$, and linear least-squares regression analysis was performed. Separate regressions were obtained for each species (WKY and SHR), further distinguished by vascular state (control and dilated). Because $\dot{Q}$ is calculated from D^2, it is natural to expect a certain degree of correlation between $\ln\dot{Q}$ and $\ln D$. However, the important result to be obtained from this regression is the value of the exponent m. An independent additional assessment of the value of k can be obtained based on the following consideration. If $\dot{Q} = kD^m$ (i.e., $V_m\pi D^2/4 = kD^m$), then the mean velocity is $V_m = (4/\pi)kD^{m-2}$ and for $m = 3$, $V_m = (4/\pi)kD$. Thus a regression of the measured (rather than calculated) quantities is anticipated to be linear with a slope $(4/\pi)k$. Additionally, because the wall shear rate (S) is related to V_m via $S = 8 (V_m/D)$ the consequence of $m = 3$ is an S value that is constant throughout the vascular bed, having a value equal to $(32/\pi)k$.

THEORETICAL ANALYSIS

The experimental data is a series of paired $\dot{Q}$ and D values that, when handled as described in the previous section, yield empirically determined values for k and m. Murray's (18) optimization strategy provides a value for m ($m = 3$) that can be compared with the corresponding experimentally determined value. However, no comparison value for k is available. The purpose of the following development is to provide an independent estimation of the value of k. Intrinsic to this development is the concept that the cost of operation of a physiological system tends to be a minimum and that an appropriate measure of this cost is the energy expenditure required to fulfill a given physiological function.

It is assumed that a certain blood flow ($\dot{Q}$) is prerequisite for the fulfilling of the physiological function of the microvasculature under study. Subject to this constraint, the relationship between $\dot{Q}$ and D, which minimizes the energy-equivalent cost of the sum of the vascular volume and hydraulic power expenditure, must be found. The vascular volume is divided into two components: the blood volume (B) and the volume of the wall material of the vessels (w), which contain that blood. For purposes of formulating the cost function it is convenient to express these quantities in terms of power equivalents. Thus we may write a cost function (C) in terms of the hydraulic power (H), B, and W as in *Eq. 1* in which K_b and K_w are in units of energy/time/volume

$$C = \mathrm{H} + K_b\mathrm{B} + K_w\mathrm{W} \qquad (1)$$

Based on the local applicability of Poiseuille's law for each vessel segment of length (L), this cost function may be written as *Eq. 2* in which η is the blood viscosity and h the vessel wall thickness

$$C = \frac{128}{\pi}\frac{L}{D^4}\eta\dot{Q}^2 + \frac{\pi}{4}K_bD^2L + \pi hK_wDL \qquad (2)$$

Recent evidence suggests an almost linear dependence of h on D in the rat microvasculature (4) thereby allowing the approximate formulation that $h = aD$, in which the constant of proportionality (a) is given approximately by 0.1. Using this in *Eq. 2*, we may write a cost function per unit vessel length (C') as in *Eq. 3*

$$C' = \frac{128}{\pi}\frac{\eta}{D^4}\dot{Q}^2 + \pi\left(\frac{K_b}{4} + aK_w\right)D^2 \qquad (3)$$

Minimization of C' with respect to D leads to the flow-diameter relationship given by *Eq. 4*

$$\dot{Q} = \left[\left(\frac{\pi}{32}\right)^2\frac{K_b + 4aK_w}{\eta}\right]^{1/2}\mathrm{D}^3 \qquad (4)$$

Calling the bracketed term k^2, we have the relationship $\dot{Q} = kD^3$, which, after using $a = 0.1$, shows that

$$k = \frac{\pi}{32}\left(\frac{K_b + 0.4\ K_w}{\eta}\right)^{1/2} \qquad (5)$$

The approximate theoretical value of k is seen to depend on the energy cost of both blood and wall volume maintenance and on blood viscosity. To obtain a numerical value for k to subsequently compare with that found from the experimental measurements, estimates of K_b, K_w, and η must be made. For this purpose we proceed as follows.

The energy cost of blood and wall volume maintenance are expressed in terms of their respective O_2 consumptions and converted to energy consumed per unit volume per unit time. The three main blood cellular constituents, red blood cells (RBC), white blood cells (WBC), and platelets (pl) are considered separately, and the sum of their respective energy consumptions K_{RBC}, K_{WBC}, and K_{pl} are equated to K_b. Numerical data for all calculations are for the rat, and with small error the mass density of cellular components and vessel wall is taken as unity. Most data in the literature quote O_2 consumption rates for individual tissues as microliters of O_2 consumed per milligram of tissue per hour. Conversion of these rates to cgs units requires multiplication by the factor 5.82×10^4 to yield the desired unit of $erg \cdot g^{-1} \cdot s^{-1}$ based on the energy equivalent of 1 g-cal of 4.186×10^7 ergs, and the approximate equivalence of 1 μl O_2 consumption equal to 5×10^{-3} g-cal. In units of microliters of O_2 per milligram per hour, the following rate constants are found in the literature (1): RBC 0.04, WBC 9, and platelets 6. To find the total volume of each cellular component contained per milliliter of whole blood, the following concentrations, in units of number per milliliter, are found in the literature (5): RBC 8.4×10^9, WBC 7.8×10^6, and platelets 7×10^7 and subsequently multiplied by the cellular volume of each respective component. For the RBC this volume is obtained from the literature (5), for the WBC it is estimated assuming a spherical shape and the average diameter of 10 μm, and for the platelet it is taken as 5 μm^3 extrapolated from the human value of 7–8 μm^3 (21). In units of micrometers cubed then, these cellular volumes are RBC 50, WBC 523, and platelets 5. Based on this numerical data, the calculated values for energy consumption of each cellular component in units of ergs per gram per second $\times 10^3$ are K_{RBC} 0.98, K_{WBC} 2.14, and K_{pl} 1.22, yielding a value for the energy rate constant for whole blood of $K_b = 4.34 \times 10^3$ $erg \cdot cm^{-3} \cdot s^{-1}$. The corresponding value for the vessel wall (K_w) is obtained using data obtained from the rat aorta (1), indicating an O_2 consumption of 1.03 $\mu l \cdot mg^{-1} \cdot h^{-1}$ which when expressed in cgs units, yields $K_w = 59.9 \times 10^3$ $erg \cdot cm^{-3} \cdot s^{-1}$. Using the numerical values for K_b and K_w in *Eq. 5* and with η expressed in centipoise, we obtain the expression for k as in *Eq. 6* below

$$k = 98(2.83/\eta)^{1/2} \qquad (6)$$

No clear choice of the value of viscosity to be used in *Eq. 6* is available. However, we may estimate an upper and lower bound in the following manner. Measurements of the in vivo hematocrit in sequential microvessels of the cat mesentery (10) reveal a decrease in the ratio (H_r) of microvessel hematocrit to systemic hematocrit with decreasing vessel diameter. Using their data (Table 1, p. 307), we have found a linear regression equation relating H_r to vessel diameter D to be $H_r = 0.00966\ D + 0.140$ ($r = 0.958$, $P < 0.001$) with D in micrometers. Measurements in our laboratory (12) have shown that the systemic hematocrit of the WKY and SHR groups are not different and have an average value of 40%. Armed with this information, we can estimate the microvessel hematocrit $H\mu$ as $H\mu = 0.0039\ D + 0.056$ cP. In vitro whole blood viscosity is a nonlinear function of the hematocrit (H) at any given shear rate. An adequate characterization of this dependence at high shear rates is given by the relation $\eta = \eta_p[1 + 2.5\ H/(1 - H)]$ (13), in which η_p is the plasma viscosity with mean value of 1.28 cP (9). Using the relationship for $H\mu$ as a function of D in this equation, we can estimate the blood viscosity in the largest (83 μm) and smallest (7 μm) average vessel diameter used in the present study to be 2.42 and 1.57 cP, respectively. Using these values in *Eq. 6* provides lower and upper bound estimates on k to be 92 and 132, respectively.

RESULTS

Figure 2 shows the results obtained for each of 160 paired $\dot{Q}$ and D values plotted for convenience in double

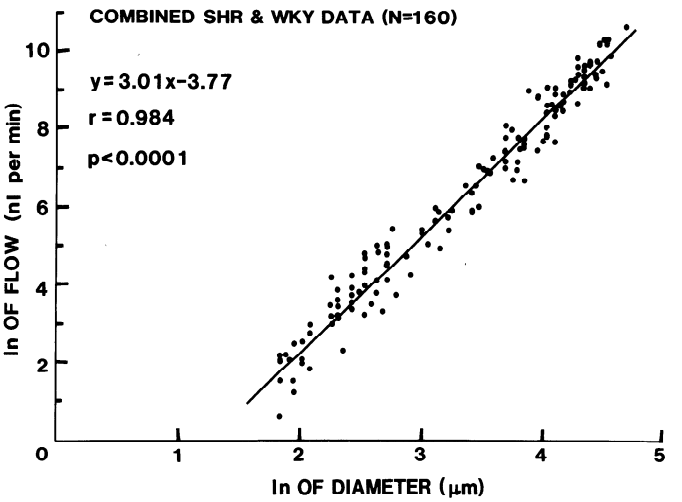

FIG. 2. Data and regression line obtained for 160 paired flow-diameter measurements in combined SHR and WKY groups. Values of m and k obtained from this data show flow ($\dot{Q}$) and diameter (D) to be linked by $\dot{Q} = 417D^{3.01}$ $cm^3 \cdot s^{-1}$.

TABLE 1. *Parameters of equation $\dot{Q} = kD^m$ determined by regression analysis for cremaster microvasculature*

Group	n	Parameters		Statistics	
		k	m	r	CI
WKY/SHR	160	417	3.01	0.984	2.86–3.14
$WKY_{c\&d}$	80	361	2.98	0.986	2.83–3.13
$SHR_{c\&d}$	80	480	3.04	0.983	2.82–3.24
WKY_c	40	200	2.89	0.984	2.60–3.18
WKY_d	40	602	3.05	0.988	2.80–3.32
SHR_c	40	475	3.05	0.982	2.75–3.35
SHR_d	40	352	2.97	0.981	2.85–3.15

See text for explanation of $\dot{Q} = kD^{-m}$. n, number of paired flow and diameter determinations; c, control state; d, dilated state; r, correlation coefficient of logarithmically transformed data; CI, confidence interval for exponent m at the 99.9% level.

logarithmic fashion with $\dot{Q}$ in nanoliters per minute and D in micrometers. The solid line drawn through the data is the regression equation, which in the units utilized, is given by $\ln(\dot{Q}) = 3.01 \ln(D) - 3.77$. The coefficient, 3.01, defines the value of m obtained from all paired data. The k value corresponding to this relationship is found as the inverse ln of the nonrounded value (−3.775) yielding a k^* value of 0.02293. Conversion of this value to one corresponding to cgs units is obtained by expressing nanoliters per minute and micrometers in cgs units and using the relation $k(\text{cgs}) = k^* (\dot{Q}_{\text{cgs}})/(D_{\text{cgs}})^m = k^* (18{,}200) = 417$. The corresponding regression equation when $\dot{Q}$ and D are expressed in cgs units is given as $\ln(\dot{Q}) = 3.01 \ln(D) + 6.03$. Table 1 summarizes the experimentally determined parameters of the equation $\dot{Q} = kD^m$ ($\dot{Q}$ and D in cgs units) and the pertinent statistics for *1*) total data graphed in Fig. 2 ($n = 160$), *2*) separate regression analyses performed by treating WKY and SHR as separate groups ($n = 80$), and *3*) these groups further broken down with respect to the vascular state (control state or dilated state, $n = 40$). The value for k from all paired data (417) has an associated 99.9% confidence integral of 331–503. The separation of the experimental groups by class and by vascular state yields k values ranging from 200 to 602. However, these differences do not prove to be statistically significant. Independent determinations of k using all the paired values of V_m and D produce the regression equation $V_m = 585D - 0.107$ cm/s ($r = 0.85$, $P < 0.001$), from which a value of $k = (\pi/4)585 = 459$ is obtained which is consistent with the variance of k when computed from the $\dot{Q}$-D regression.

DISCUSSION

The value of the exponent. The most direct and accurate approach to ascertain the in vivo applicability of a relationship of the form $\dot{Q} = kD^m$ is to simultaneously determine $\dot{Q}$ and D. This approach was adopted in the present study, and the data strongly suggest an almost third-power dependence of flow on diameter ($m = 3.01$). As summarized in Table 1 when all paired measurements of vessel D and $\dot{Q}$ are analyzed, the value of the exponent m in the equation $\dot{Q} = kD^m$ is determined to be between 2.86 and 3.14 with a probability of 99.9%. The fact that the value of m was insignificantly dependent on specific animal strain used (WKY or SHR) or the vascular state of the cremasteric bed of these strains implies a somewhat general relationship.

The precise value of m found depends on the accuracy with which both $\dot{Q}$ and D can be determined under the present in vivo conditions. The dual-slit/cross-correlation method herein employed to determine center-line velocity is currently the best available procedure, but some would argue that it provides only an estimate of velocity, and thereby an estimate of volume flow is ultimately determined. In vitro calibrations of the system utilized in our laboratory indicate a fractional error in velocity of less than ±4% over the velocity range of 2–100 mm/s and a corresponding diameter measurement error of less than ±6% over the diameter range of 7–100 μm. The worst case occurs in the smallest vessels. Thus for the smallest arterioles measured (7 μm) the true value may lie between 6.55 and 7.45 μm according to our in vitro calibration as described in METHODS. In view of the calculated flow dependence on the square of the diameter, an error in calculated flow of approximately ±16% may be present in the smaller vessels. To estimate the effect of such random errors on the value of m and k, two worst-case conditions were considered. In each of these it was assumed that the maximum error in velocity (±4%) occurred simultaneously with the maximum error in diameter (±6%). Under these conditions all 160 data points were reanalyzed and values for k and m determined. The principal effect of these assumed errors was on the value of k, which for errors of +6% and −4% in velocity and diameter, respectively, was equal to 302 and for corresponding errors of −6% and 4% was 592. Determinations of m for each of these error conditions showed its value varying only in the third decimal point, from 3.013 to 3.012.

Indirect assessments of the exponent m in the absence of blood flow measurements may be obtained by comparing the diameter relationships predicted by the functional relationship $\dot{Q} = kD^m$ with measured values. Thus if $\dot{Q} = kD^m$ then it can be shown that the diameter of a parent vessel (D_o) is related to the diameters of its n branches (D_i) by *Eq. 7*

$$D_o^m = \sum_{i=1}^{n} D_i^m \qquad (7)$$

Making use of this fact, diameter measurements obtained from postmortem human coronary arteriograms (7) yielded a mean ± SD value for the exponent m of 3.2 ± 1.6 for the left main coronary artery and its branches in normal vessels (diam range 1.0–3.3 mm). Though the mean value is consistent with that obtained in the present study the standard deviation these workers report is quite large. Using a similar analytical technique, Suwa and co-workers (23) obtained an average value of $m = 2.7$ from data obtained from acrylic resin arterial casts of a variety of human organs. The effect of the injection process may account for the slightly smaller value of m than was here determined. An attempt to clarify the issue further using photographs of the human retinal vasculature (31) proved unsuccessful due to inadequate resolution. Notably, however, cast measurements of sheep bronchi diameters (6) yielded a value of 2.98 for the exponent m. Taken together, the direct and indirect determinations of the exponent m appear to strongly support the third-power dependence of $\dot{Q}$ on D as a general average property of the terminal vasculature.

The value of k. The other parameter in the relationship $\dot{Q} = kD^m$, the k value, proved to be less uniform than m in the cremaster microvasculature. By use of the flow-diameter regression technique, the calculated absolute value of k depends on the extrapolation of the regression line with slope m to a region beyond that for which experimental data are available. Thus small differences in slope tend to be magnified and result in what appears to be k value variability inconsistent with the m value uniformity. In spite of this expected variation, analysis of the regression equations for SHR and WKY groups with vascular state as separate classes show no statistical

difference among the k values. Thus the value $k = 417$ reflects an overall proportionality constant applicable to the cremaster microvasculature. The physical significance of k is twofold. On the one hand, it may be interpreted purely as an empirically determined parameter that links $\dot{Q}$ and D^m. On the other hand, when viewed as a parameter associated with the optimality analysis, k is theoretically related to the per unit time energy consumption of blood and vessel wall.

The upper bound on the theoretical estimate of k in the present study was 132, which is more than a factor of three less than the value of k determined from the experimental data. An explanation that may account for this difference is that the contribution to the total cost function of H, B, and W (*Eq. 1*) may not be equally weighted as was intrinsically assumed in the theoretical development. If, for example, due to differences in efficiency of metabolism, the energy cost for vessel blood and wall volume were greater than the cost of hydraulic power by a factor of λ, then the theoretial value of k would be increased by a factor of $\lambda^{1/2}$. Data are not as yet available to make such determinations with any degree of confidence. In spite of the discrepancy between the theoretically estimated value ($k = 132$) and the value found from the experimental data ($k = 417$) the order of magnitude agreement is consistent with the optimality theory in view of the uncertainty of the numerical data used to calculate the theoretical value of k. The calculation of the wall energy consumption rate constant, K_w, was based on data for the rat aorta. Because the relative composition of the aorta is different than found in the arterioles, it is likely that a discrepancy is to be found in this extrapolation. Because the relative amount of vascular smooth muscle is greater in the smaller vessel, it is likely that the extrapolation from aorta to arteriole yields an underestimation of K_w and thereby an underestimation of k. However, without specific data on O_2 utilization of these smaller vessels, the estimates herein used must suffice.

Implication for in vivo vascular network. The finding that $\dot{Q} = kD^{3.01}$ describes the in vivo flow-diameter conditions does not imply that flow in an individual vessel is determined by $D^{3.01}$. Flow in any particular vessel is determined by the standard hemodynamic principles applicable to the microcirculation, and the present results do not negate the applicability of Poiseuille's law. The reconciliation of these apparently contradictory concepts requires one to distinguish between single-vessel hemodynamics and the composite hemodynamics associated with an entire vascular network (26). A schematic representation of the five arterial branching orders studied (Fig. 1) may serve to clarify this point. With the assumption of the applicability of Poiseuille's law, flow in any of the arterial segments shown is given by

$$\dot{Q}_i = \frac{\pi}{128} \frac{p'_i}{\eta_i} D_i^4 \qquad (8)$$

in which p'_i is the pressure gradient ($\Delta p_i/L_i$) within an ith order vessel segment of length L_i, η_i is the blood viscosity, and D_i the vessel diameter. If, for example, the average pressure gradient of the fourth-order vessel, ($p_x - p_y$)/L_4, and blood viscosity were known, then the flow in it could be determined and would be proportional to D^4. It is a fact, however, that p'_i is a function of the overall distribution of vascular resistance within the microvascular bed (14, 15). The resistance distribution in turn depends on the specific vascular topography, number of vessels, their diameter distribution, and a host of other factors. The approximate third-power dependence of flow on diameter found in the present study implies that under in vivo conditions the summated effect of these multiple factors results in a ratio p'_i/η_i, which is proportional to $1/D_i$. Thus given any specific pathway the pressure drop across each of the consecutive levels of the microvascular bed Δp_i, may be expressed as

$$\Delta p_i = \frac{128}{\pi} k\eta_i \frac{L_i}{D_i} \qquad (9)$$

Therefore in spite of a vessel flow resistance proportional to $\eta L/D^4$ (Poiseuille) the distribution of pressure loss across the bed depends on $\eta L/D$.

Predictions based on applicability of $\dot{Q} = kD^3$. The applicability of the relationship $\dot{Q} = kD^3$ implies that the average pressure gradient (p') in a single vessel is a linear function of the ratio of blood viscosity to vessel diameter as expressed by *Eq. 10* below

$$p' = \frac{128}{\pi} k \frac{\eta}{D} \qquad (10)$$

The applicability of *Eq. 10* is best tested by comparison of the predicted pressure gradient with in vivo measurements of the same quantity. Though such measurements are rare, Zweifach (32) and Lipowsky and co-workers (9) have reported such data for the cat mesentery microvasculature. To perform the indicated comparison between their data and that predicted by *Eq. 10* a value of k is estimated for the cat mesentery utilizing the 42 velocity-diameter values previously reported (Fig. 5 of Ref. 33) for arterial vessels ranging from 8 to 56 μm. These data are handled exactly as the cremaster data was in the present paper, and the flow-diameter relation that emerges is given by $\ln(\dot{Q}) = 2.96 \ln(D) + 4.776$ ($r = 0.954$, $P < 0.001$) with $\dot{Q}$ and D in cgs units. From this, a value $k = 119$ is obtained. By use of a mean systemic hematocrit of 35.5% (9), a value for viscosity can be

TABLE 2. *Comparison of predicted and measured pressure gradient in microvessels of different diameter ranges*

Diameter*	Pressure Gradient†		
	Predicted	Measured‡	Measured§
60 (55–65)	1.92	1.1	2.0
40 (35–45)	2.45	1.6	4.6
20 (16–24)	4.15	3.2	4.6
7 (5–9)	10.60	8.2	14.7

* Mean diameter and range in μm. † Dyn/cm^3 × 10^4. ‡ Cat mesentery (32). § Cat mesentery (9).

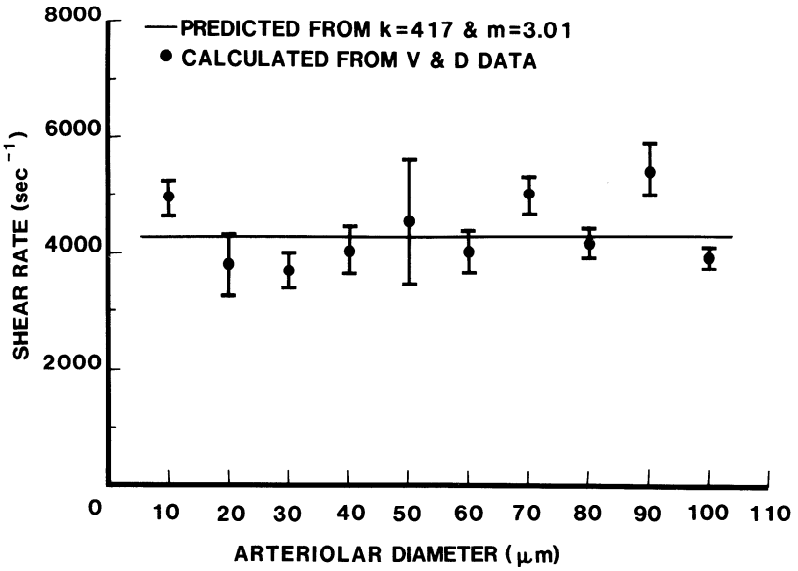

FIG. 3. Predicted constant shear rate (4,253 s^{-1}) compared with calculated values from 160 paired velocity (V) and diameter (D) measurements. Each *data point* plotted represents mean shear rate obtained for indicated vessel diameters ±5 μm. *Error bars* are ±1 SE.

calculated for any microvessel diameter as previously described and *Eq. 10* evaluated. The result of this calculation is compared with the experimental data in Table 2 for the mean diameter of the ranges indicated. It is noted that for each diameter range the predicted pressure gradient lies between the reported experimental values.

A further prediction based on the relationship $\dot{Q} = kD^3$ is that the average wall shear rate will be constant and independent of vessel diameter and as shown previously is equal to $(32/\pi)k$. In Fig. 3 this prediction is tested by comparing the calculated value of wall shear rate in all vessels measured in the rat cremaster according to the equation shear rate = $8V/D$, with that predicted on the basis of a k value equal to 417 and m value equal to 3.01. Although some scatter is evident around the predicted line of constant shear rate, the closeness of the comparison further supports the $\dot{Q} = kD^3$ relationship.

In conclusion, it appears that the relationship $\dot{Q} = kD^3$ does in fact represent a general average property of the microvascular beds dealt with. This conclusion is based on and supported by *1*) specific data of the current experiments to test this relationship, *2*) data within the literature, and *3*) on the secondary predictions and implications of the applicability of this relationship. Whether or not its in vivo applicability arises because of an overall optimality constraint may still be open to question. However, at present the defining characteristics would appear to be useful to a further understanding of those hemodynamic and microvascular processes that are adequately addressed, using this conceptual representation of the overall average properties of the vascular bed.

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