

# An Optimization Principle for Vascular Radius Including the Effects of Smooth Muscle Tone

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**ABSTRACT** An optimization principle is proposed for the regulation of vascular morphology. This principle, which extends Murray's law, is based on the hypothesis that blood vessel diameter is controlled by a mechanism that minimizes the total energy required to drive the blood flow, to maintain the blood supply, and to support smooth muscle tone. A theoretical analysis reveals that the proposed principle predicts that the optimum shear stress on the vessel wall due to blood flow increases with blood pressure. This result agrees qualitatively with published findings that the fluid shear stress in veins is significantly smaller than it is in arteries.

## INTRODUCTION

Investigators have long hypothesized that biological form is regulated by a set of physiological principles that optimize function. Recognizing the importance of mechanics in the cardiovascular system, Murray (1926) proposed a minimum work principle that led to what is now known as Murray's law. According to this principle, vascular morphology is determined by a process that minimizes the total energy cost required to maintain the blood supply and to drive the blood through the vessels. As the vascular radius increases, less energy is needed for blood flow, but more is required to maintain a larger blood volume. Optimization leads to a compromise geometry, with the lumen radius being proportional to the cube root of the volume flow rate. Over the years, this result has been confirmed by numerous experimental studies (LaBarbera, 1990).

About 50 years later, Rodbard (1975) suggested that the fluid shear stress  $\tau_w$  on the vessel wall plays a major role in regulating vascular lumen size, and Zamir (1977) showed that a constant shear stress hypothesis is consistent with Murray's law. Zamir, however, found that available experimental data did not support a uniformly constant value for  $\tau_w$  throughout the vascular system, and suggested that the variation is due to the differences in function among the various types of vessels. This conclusion, however, was based on the assumption of a constant blood viscosity. Thus Kamiya et al. (1984) examined whether the dependence of apparent viscosity on vessel radius could account for the variations in  $\tau_w$ . In the dog, cat, and rat, these investigators found that the adjusted value of  $\tau_w$  is controlled rather tightly in arteries and capillaries, lying between  $\sim 10$  and  $25$

dyn/cm<sup>2</sup>. But  $\tau_w$  was still estimated to be significantly smaller in veins ( $\sim 1$ – $6$  dyn/cm<sup>2</sup>).

In searching for a functional cause for the different magnitudes of  $\tau_w$  in arteries and veins, Pries et al. (1995) speculated that the homeostatic value for  $\tau_w$  depends locally on the blood pressure. To test their pressure-shear hypothesis, these authors estimated the shear stress  $\tau_w$  and the pressure  $p$  in the rat mesentery, using direct measurements of flow in conjunction with a theoretical model. A plot of  $\tau_w$  versus  $p$  revealed that their data for arterioles, capillaries, and venules fall essentially on a single curve (see Fig. 1). Thus the lower  $\tau_w$  in veins corresponds to their relatively lower blood pressure.

The present work examines the theoretical dependence of  $\tau_w$  on  $p$ . We postulate that vasomotor regulation of blood flow requires a significant portion of the energy needed to run an efficient cardiovascular system. Thus Murray's law is modified to include the energy cost due to maintaining smooth-muscle contraction against the distending effects of wall stress, which in turn depends on pressure and vessel geometry. Minimizing a modified cost function yields a fluid shear stress that increases with the pressure. The theoretical predictions agree qualitatively with published data on shear stresses in blood vessels.

## OPTIMIZATION PRINCIPLE

A segment of a blood vessel is modeled as a thin-walled tube of radius  $R$ , thickness  $H$ , and length  $L$ . Blood flows through the tube with a mean pressure  $p$  and volume flow rate  $Q$ . In an average sense, the flow is treated as laminar and steady, with the details of the oscillatory flow pattern ignored. Moreover, as a first approximation, deformations are assumed to be small. The total power required to sustain a regulated flow of blood through the segment is assumed to be

$$P = P_f + P_b + P_w \quad (1)$$

where  $P_f$  is the power required to drive the flow of blood,  $P_b$  is the metabolic power required to maintain the blood sup-

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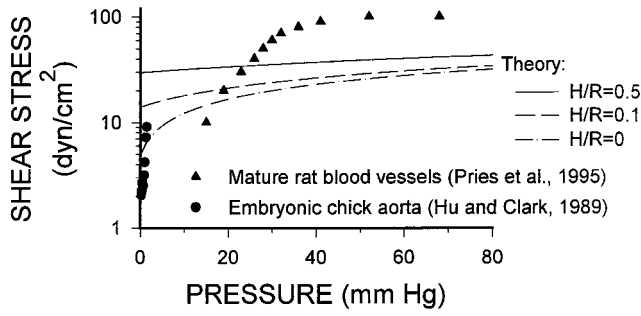


FIGURE 1 Fluid shear stress as a function of blood pressure in vessels of the mature rat mesentery and the aorta of the chick embryo. Theoretical results for three values of the relative wall thickness  $H/R$  are compared to experimental data of Pries et al. (1995) for the rat and to calculations based on the measurements of Hu and Clark (1989) for the chick (Table 1). The trends in the theoretical and experimental results are qualitatively similar, as the shear stress increases nonlinearly with pressure.

ply, and  $P_w$  is the power required to maintain the vessel wall, including medial smooth muscle tone. In the following paragraphs, expressions for each term in Eq. 1 are derived.

For Poiseuille flow, the power needed to overcome the viscous drag on the blood flow through the vascular segment is

$$P_f = 2\pi L \int_0^R \tau \dot{\gamma} r dr \quad (2)$$

Here,

$$\dot{\gamma} = \frac{4rQ}{\pi R^4} \quad (3)$$

is the fluid shear-strain rate at a radius  $r$  and

$$\tau = \mu \dot{\gamma} \quad (4)$$

is the shear stress, where  $\mu$  is the blood viscosity (Fung, 1996). Substituting Eqs. 3 and 4 into Eq. 2 and integrating yields

$$P_f = \frac{8\mu Q^2 L}{\pi R^4} \quad (5)$$

The power required to maintain the blood supply is assumed to be proportional to the blood volume ( $V_b = \pi R^2 L$ ). Thus, we take

$$P_b = \pi R^2 L \alpha_b \quad (6)$$

where  $\alpha_b$  is a metabolic constant for the blood. Murray's law is based on minimizing the power given by  $P_f$  and  $P_b$ , but the vessel wall also uses energy.

The energy costs of the vessel wall include those due to basal metabolism and vasomotor tone. The basal metabolic energy is assumed to be proportional to wall volume, and experimental data indicate that the power required for smooth muscle contraction is proportional to the active fiber

stress  $\sigma_a$  (Paul, 1980). Thus the total smooth-muscle power per unit volume is

$$P_{sm} = \alpha_w + \beta_w \sigma_a \quad (7)$$

where  $\alpha_w$  and  $\beta_w$  are passive (basal) and active metabolic constants, respectively. Depending on the degree of activation, the active muscle-fiber stress is some fraction  $f$  of the total fiber stress  $\sigma$ , which contains both active and passive components. With the muscle fibers taken as primarily circumferential, Laplace's law gives

$$\sigma = pR/H \quad (8)$$

and combining Eqs. 7 and 8 (with  $\sigma_a = f\sigma$ ) yields the wall maintenance power

$$\begin{aligned} P_w &= P_{sm} V_w = [\alpha_w + \beta_w (fpR/H)] (2\pi RHL) \\ &= 2\pi R^2 L (\alpha_w \bar{H} + f\beta_w p) \end{aligned} \quad (9)$$

for the vessel segment, where  $V_w$  is the wall volume and  $\bar{H} \equiv H/R$  is the relative wall thickness.

We seek the optimal vessel geometry for given mean pressure and flow. In addition, because a blood vessel maintains an approximately homeostatic wall stress during remodeling (Liu and Fung, 1989; Matsumoto and Hayashi, 1994), Eq. 8 shows that  $\bar{H}$  is fixed in a given vessel. Hence, after substitution of Eqs. 5, 6, and 9 into Eq. 1, the minimization conditions

$$\frac{\partial P}{\partial R} = 0 \quad \frac{\partial^2 P}{\partial R^2} > 0 \quad (10)$$

give

$$\frac{Q^2}{R^6} = \frac{\pi^2}{16\mu} (\alpha_b + 2\bar{H}\alpha_w + 2f\beta_w p) \quad (11)$$

Finally, combining Eqs. 3, 4, and 11 provides the optimal fluid shear stress at the wall:

$$\tau_w \equiv \tau(R) = \frac{4\mu Q}{\pi R^3} = [\mu(\alpha_b + 2\bar{H}\alpha_w + 2f\beta_w p)]^{1/2} \quad (12)$$

For  $\alpha_w = \beta_w = 0$ , these relations agree with the results of Murray (1926) (see also Zamir, 1977). In this case, if  $\alpha_b$  and  $\mu$  are constant, the theory predicts a constant value for  $\tau_w$ . On the other hand, if  $\beta_w \neq 0$ , then  $\tau_w$  increases with the pressure.

## EXPERIMENTAL DATA ANALYSIS

### Embryonic chick aorta

Pressure and flow data are available for the blood vessels of the rat mesentery and the dorsal aorta of the chick embryo. For the rat, Pries et al. (1995) provided plots of  $\tau_w$  versus  $p$ . For the dorsal aorta of the chick embryo, we estimated  $\tau_w$  by using the data of Hu and Clark (1989), who measured blood-flow velocity and geometry during developmental

stages 12–29 (days 2–6) of a 46-stage (21-day) incubation period. These stages cover the period of primary cardiac morphogenesis, with sustained blood flow beginning at about stage 12 (Romanoff, 1960).

With the average flow velocity  $U$  given by pulsed Doppler ultrasound, substituting the flow rate  $Q = (\pi R^2)U$  into Eq. 12 yields the average wall shear stress:

$$\tau_w = \frac{4\mu U}{R} \quad (13)$$

which was used to compute  $\tau_w$  (Table 1) once the effective viscosity  $\mu$  was determined as described below. For blood pressure, we used their measurements in the vitelline artery, which is just downstream of the aorta (Table 1).

### Parameter values

For a given blood pressure and vessel geometry, computing the optimal wall stress from Eq. 12 requires values for the blood viscosity  $\mu$  and the metabolic constants  $\alpha_b$ ,  $\alpha_w$ , and  $\beta_w$ . The experimental calculation requires a value for  $\mu$ , in addition to the measurements of  $U$  and  $R$ .

Effective blood viscosity depends on vessel diameter (Fahraeus-Lindquist effect) and hematocrit (Pries et al., 1992). To our knowledge, the effective viscosity of embryonic chick blood has not been measured, but some data are available for the mature duck (Gaehtgens et al., 1981a,b). Measured vessel diameters (Table 1) and calculations of chick embryo hematocrit based on the data of Romanoff (1960) suggest that viscosity can be taken as roughly constant during the studied stages. Thus we used  $\mu = 3$  cp as a first approximation in all of our calculations for the chick. For the rat, Pries et al. (1995) included the effects of both vessel diameter and hematocrit in their measurements, but they did not provide enough information to enable us to adjust the values for  $\mu$  used in our theoretical computations. Thus the theoretical shear stress for the rat was also computed using a constant viscosity of  $\mu = 3$  cp.

Relatively limited information is available for determining the metabolic parameters. To estimate the blood maintenance power, we used the following published data for red

blood cells (RBC), white blood cells (WBC), and platelets (PL): 1) oxygen consumption rates ( $\mu\text{mol O}_2/\text{h}/10^{11}$  cells or thrombocytes), RBC 2.7, WBC 4000, PL 86.3 (Diem and Lentner, 1970); 2) concentrations (number/ml rat blood), RBC  $8.4 \times 10^9$ , WBC  $7.8 \times 10^6$ , PL  $7 \times 10^7$  (Mayrovitz and Roy, 1983). Combining these numbers with the conversions  $2.09 \times 10^5$  erg/ $\mu\text{l O}_2$  and  $0.0447$   $\mu\text{mol O}_2/\mu\text{l}$  yields the following metabolic rates (erg/ml-s): RBC 295, WBC 405, PL 78.5. Thus the total maintenance power for rat blood is  $\alpha_b = 778$  erg/ml-s, which is the value used in all computations.

The values of  $\alpha_w$  and  $\beta_w$  were determined using the basal and stimulated ATP utilization rates, respectively, for smooth muscle reported by Paul (1980). With an energy production of 31.8 kJ/mol ATP and an efficiency of oxidative phosphorylation of 42% (Weibel, 1984), we obtained values of  $\alpha_w$  and  $\beta_w$  for the rat portal vein, the bovine mesenteric vein, and the porcine carotid artery (Table 2). The value of  $\alpha_w$  for the rat portal vein is about half that estimated for the rat aorta by Mayrovitz and Roy (1983).

According to Paul (1980), the metabolic rates for smooth muscle depend roughly on the inverse of animal size. Thus because data are not available for the rat mesentery and chick aorta, we used the values for  $\alpha_w$  and  $\beta_w$  for the rat portal vein in all calculations, unless stated otherwise.

### Other assumptions

Although it is difficult to generalize results for diverse biological systems, observing some general trends is useful. The results presented in this paper are based on the following approximations:

1. For a particular type of blood vessel, e.g., the aorta, the relative wall thickness  $\bar{H} = H/R$  is similar across species. In a given animal, however,  $\bar{H}$  varies inversely with vessel size (Fung, 1996).

2. Large-vessel blood viscosity is similar in magnitude in all animals. Because of the Fahraeus-Lindquist effect, however, the effective viscosity is lower in smaller vessels (Fung, 1993).

**TABLE 1** Experimental results for embryonic chick aorta

Stage	Days	$R^*$ (mm)	$U^*$ (mm/s)	$Q$ (mm <sup>3</sup> /s)	$\tau_w$ (dyn/cm <sup>2</sup> )	$p^*$ (mmHg)	$f_H^*$ (bpm)	$N_w$
12	2	0.051	0.860	0.007	2.03	0.28	103	0.096
14	2¼	0.102	1.89	0.061	2.23	0.40	114	0.203
16	2½	0.124	2.77	0.135	2.67	0.49	122	0.257
18	3	0.144	2.99	0.194	2.50	0.71	146	0.324
21	3½	0.161	4.22	0.342	3.15	0.90	155	0.373
24	4	0.183	6.40	0.674	4.20	1.03	172	0.449
27	5	0.190	11.5	1.30	7.23	1.29	183	0.480
29	6	0.203	15.3	1.99	9.06	1.51	208	0.547

\*Mean values from Hu and Clark (1989).

$R = 0.9R_0$ , where  $R_0$  is the measured outer vessel radius;  $Q = \pi R^2 U$ ;  $\tau_w$  was computed using Eq. 13;  $N_w = R(2\pi f_H \rho / \mu)^{1/2}$ , where  $\rho = 1$  g/cm<sup>3</sup> ( $\mu = 3$  cp in all calculations).

**TABLE 2 Metabolic constants for vessel wall**

	$\alpha_w$ (erg/cm <sup>3</sup> -sec)	$\beta_w$ (s <sup>-1</sup> )
Rat portal vein	$2.88 \times 10^3$	0.158
Bovine mesenteric vein	$1.21 \times 10^3$	0.0177
Porcine carotid artery	$7.64 \times 10^3$	0.00872

3. In a given animal, the metabolic parameters are similar in all blood vessels. The metabolic rates, however, vary inversely with animal size (Paul, 1980).

4. Average blood pressure is similar in most mammalian species (McMahon, 1984). In a given animal, the pressure decreases as the blood passes through the arterioles, capillaries, and veins (Fung, 1996).

5. Passive stresses, which may contribute 20% or so to the total wall stress in an active vessel (Paul, 1980), are ignored ( $f = 1$ ).

## RESULTS

Validating the proposed optimization principle with experimental measurements is crucial. However, because of incomplete physiological data, quantitative correlation of theoretical and experimental results is quite limited. Thus we examine qualitative trends while making quantitative comparisons where possible. Note that the parameters contained in Eq. 12 are the viscosity  $\mu$ , the relative wall thickness  $\bar{H}$ , the blood pressure  $p$ , and the metabolic parameters  $\alpha_w$  and  $\beta_w$ . In general, only one parameter is varied at a time.

### Optimal wall shear stress increases with blood pressure

Qualitatively, this prediction is consistent with the relatively low values of  $\tau_w$  found in veins as compared to arteries (Kamiya et al., 1984) and with the pressure-shear hypothesis of Pries et al. (1995).

To check this prediction quantitatively, we first compute  $\tau_w$  in large arteries and veins using  $\mu = 3$  cp,  $\bar{H} = 0.1$ , and the data in Table 2. With  $p = 100$  mmHg for arteries, Eq. 12 yields  $\tau_w = 38.0$ , 15.4, and 11.8 dyn/cm<sup>2</sup> for the rat, cow, and pig, respectively. With  $p = 2$  mmHg for veins, the corresponding values are  $\tau_w = 14.9$ , 9.9, and 8.4 dyn/cm<sup>2</sup>. These numbers can be compared to the values 12.0 and 6.3 dyn/cm<sup>2</sup> reported by Kamiya et al. (1984) for the dog aorta and vena cava, respectively. The theoretical values for the pig agree relatively well with those for the dog, as may be expected because of the relatively similar sizes of these animals.

Next, theoretical values of the shear stress  $\tau_w$  computed from Eq. 12 are compared to the experimental data of Pries et al. (1995) for vessels of the mature rat mesentery and to the results for the dorsal aorta of the chick embryo given in Table 1 (Fig. 1). The experimental results for the rat repre-

sent a conglomeration of data from arterioles, capillaries, and venules of various diameters.

Theoretical results are shown for three values of  $\bar{H}$  (Fig. 1). The predicted trend of the  $\tau_w$  versus  $p$  curve is similar to the experimental results for the rat mesentery, as the shear stress increases at low pressures and tends to level off at higher pressures. However, the theoretical values for  $\tau_w$  are too high for relatively low pressures and too low at high pressures, and the shear stress continues to increase like  $p^{1/2}$  at high pressures, rather than approaching the asymptotic value indicated by the experimental data. The qualitative agreement improves as  $\bar{H}$  decreases.

For the embryonic chick aorta, the theoretical results for  $\bar{H} = 0$  agree quite well with the measured magnitude of  $\tau_w$  (Fig. 1). Note that  $\tau_w$  generally increases with time during development (Table 1). Calculations using the flow and geometry data of Hughes (1937) for extraembryonic vessels in the day 2–3 chick embryo give similar but somewhat smaller values for the shear stress (results not shown).

### Optimal wall shear stress increases with the relative vessel wall thickness

For  $p = 100$  mmHg and the metabolic parameters for the pig, Eq. 12 gives  $\tau_w = 11.8$ , 13.6, and 17.9 dyn/cm<sup>2</sup> for  $\bar{H} = 0.1$ , 0.2, and 0.5, respectively. Because  $\bar{H}$  generally increases as the artery radius decreases (Fung, 1996), these numbers compare reasonably well with the reported values  $\tau_w = 12.0$ , 10.4, and 18.6 dyn/cm<sup>2</sup> for the aorta, large arteries, and small arteries of the dog (Kamiya et al., 1984). In arterioles, Kamiya et al. (1984) estimated  $\tau_w = 14.1$  dyn/cm<sup>2</sup>; the lower value (relative to small arteries) reflects the smaller pressure and effective viscosity in these vessels.

### Optimal wall shear stress increases with the rate of smooth muscle metabolism

This prediction is consistent with the inverse relation found between  $\tau_w$  and animal size (Langille, 1993), because smaller animals generally have higher smooth-muscle metabolic rates (Paul, 1980). There appear to be some inconsistencies in these trends, however, both in the reported values of  $\alpha_w$  and  $\beta_w$  (see Table 2 for the cow and pig) and in the measured values for  $\tau_w$  (Langille, 1993). The reasons for these discrepancies are not clear.

## DISCUSSION

The main finding of the present study is that the pressure dependence of the fluid shear stress  $\tau_w$  in blood vessels may be explained by an optimization principle that minimizes the total energy required to 1) drive the blood flow, 2) maintain the blood supply, and 3) maintain a regulatory smooth-muscle tone in the vessel walls. The first two of these effects lead to Murray's law, which, for constant blood viscosity  $\mu$  and blood maintenance factor  $\alpha_b$ , predicts



a constant shear stress throughout the vascular system (Murray, 1926; Zamir, 1977). This prediction, however, is confounded by the relatively low value for  $\tau_w$  in veins (Kamiya et al., 1984). Including vasomotor effects appears to alleviate this discrepancy between theory and experiment, while providing a possible functional explanation for the dependence of  $\tau_w$  on blood pressure (Eq. 12).

Previous studies have shown that increased pressure or decreased flow rate (and shear stress) induces a decrease in vessel radius, whereas decreased pressure or increased flow rate leads to an increase in radius (Rodbard, 1975; Johnson, 1980; Langille, 1993). The present model is consistent with the pressure-shear hypothesis of Pries et al. (1995), who postulated that these effects are coupled. Our analysis suggests that the homeostatic value for  $\tau_w$  is set by the pressure according to Eq. 12. Then, for a given flow rate  $Q$ , the vessel radius adjusts according to Poiseuille's formula to maintain this optimum value for  $\tau_w$ . Consequently, the regional variation of pressure in the vascular system accounts for the different homeostatic values for  $\tau_w$  in arteries and veins.

## Implications

Implicit in our analysis is the assumption that all blood vessels, regardless of function, follow the same optimization principles throughout life. This idea is consistent with the qualitative agreement between our theory and available experimental data and with our previous work on modeling of cardiovascular growth (Lin and Taber, 1995; Taber and Eggers, 1996). Moreover, during vasculogenesis in the embryo, the structures of arteries and veins are similar until they differentiate, as their loading conditions diverge (Murphy and Carlson, 1978), indicating that vascular morphogenesis depends in part on mechanical effects. According to the present theory, these mechanical factors include both blood pressure and flow.

The relative similarity in the magnitude of  $\tau_w$  across species (Kamiya et al., 1984; Langille, 1993) and age range (Fig. 1) is remarkable in view of the vast differences in flow rate. Compare, for example, the values for  $Q$  of  $10^5 \text{ mm}^3/\text{s}$  in an adult human and  $2 \text{ mm}^3/\text{s}$  in the 6-day chick embryo (Table 1). More than a century ago, Thoma (1893) speculated that the increasing flow rate drives vascular growth during development, and our calculations support the view that the fluid shear, as modulated by blood pressure, is the specific mechanical factor that regulates the increase in lumen size.

It is known that mature blood vessels adapt to perturbations in pressure and flow by altering their morphology (Rodbard, 1975; Johnson, 1980; Langille, 1993). The acute response is due to active contraction or relaxation of the medial smooth muscle. Then, if the altered loading conditions persist, the vessel remodels to attain a similar but "permanent" change in geometry. Our model is based on the hypothesis that vessel geometry is determined by the acute

response as a worst-case basis for energy consumption. This hypothesis is consistent with 1) the finding of Rodbard (1975) that vessel radius depends on peak, rather than resting, flow rate; and 2) the relatively small energy cost of maintaining basal smooth muscle tone in arteries (Paul, 1980). Remodeling, then, is an adaptation that returns vascular tone to the basal level.

In light of these observations, it is important to note that the aorta of the early chick embryo does not yet contain smooth muscle. Because muscle tone is a major feature of our analysis, the reasonable agreement between the theoretical and experimental results (Fig. 1) may be fortuitous. On the other hand, it may be that construction rules for vascular morphogenesis are set during early development, before the smooth muscle differentiates.

## Limitations

Although the theoretical values of  $\tau_w$  are in qualitative agreement with measured data for blood vessels of some species, the poor quantitative correlation with the results of Pries et al. (1995) is somewhat disconcerting (Fig. 1). If the proposed optimization principle is valid, then the possible explanations for this discrepancy include variations in effective viscosity in the studied vessels and the mechanical effects of the mesenteric tissue surrounding the vessels.

In addition, the present theory neglects several factors that may limit its usefulness. For example, the analysis ignores nonlinear behavior due to large-deformation, thick-wall effects, and the details of the vessel microstructure. Furthermore, the oscillatory flow pattern and local changes in flow characteristics near branches and in capillaries are neglected. Oscillatory flow can be characterized by the Womersley number  $N_w = R(2\pi f_H \rho / \mu)^{1/2}$ , where  $f_H$  is the heart rate and  $\rho = 1 \text{ g/cm}^3$  is the mass density of the blood (Fung, 1996). In the chick aorta, the value of  $N_w$  increases during development, but remains less than unity at stage 29 (Table 1), and we estimate that  $N_w < 0.1$  in the rat mesentery. These relatively small values indicate that viscous effects dominate inertial effects in these vessels. Thus our assumption of Poiseuille flow, which assumes negligible inertia, likely provides a good approximation for the average flow characteristics. All of these factors likely influence the results quantitatively but not qualitatively.

On the other hand, some authors speculate that the varying functional requirements of blood vessels, such as the metabolic demands of the surrounding tissues, dictate their structure (Zamir, 1977). Although this idea continues to have merit, the present theory does not account for these effects.

Despite these limitations and in view of the fact that Eq. 12 contains no adjustable parameters (if the estimated values are valid), it seems significant that the magnitudes of the theoretical and experimental values for  $\tau_w$  agree as well as they do.

In conclusion, we postulate that lumen size in the cardiovascular system is governed by a single optimization prin-

ciple throughout the lifetime of an organism. Minimizing the total energy cost of driving and maintaining a regulated supply of blood suggests that a major controlling factor is the fluid shear stress, the homeostatic value of which is set by the blood pressure. Although available experimental data tentatively support this view, more measurements are needed to confirm this hypothesis. Moreover, the precise signaling mechanism on the molecular level remains to be determined.

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