Adaptive regulation of wall shear stress to flow change in the canine carotid artery

AKIRA KAMIYA AND TATSUO TOGAWA
Research Institute of Applied Electricity, Hokkaido University, Institute for Medical and Dental Engineering, Tokyo Medical and Dental University, Tokyo, Japan

KAMIYA, AKIRA, AND TATSUO TOGAWA. Adaptive regulation of wall shear stress to flow change in the canine carotid artery. Am. J. Physiol. 239 (Heart Circ. Physiol. 8): HM-H21, 1980.—To study the adaptive response of the vascular wall to blood flow changes, an arteriovenous shunt was constructed between the common carotid artery and the external jugular vein in 12 dogs. Six to eight months postoperatively, the arterial internal radius (r) was determined by angiography and/or the use of pressure-volume relationship. The results showed that r increased with increased flow load (f) and vice versa. Wall shear rate (γ) was calculated from γ = 4f/(πr²), assuming laminar flow. The value of γ, initially proportional to f, had recovered almost to the control level (within 15%) due to the vessel dilatation or atrophy during the chronic experiment, when f was less than 4 times the control. Transendothelial protein permeability, evaluated at the T-1824-stained surface by a reflectometric method, also showed a close correlation with permeability, evaluated at the T-1824-stained surface by a dilatation or atrophy during the chronic experiment, when f was less than 4 times the control. A local autoregulatory mechanism of wall shear stress involving protein turnover in the vascular wall is suggested.

arteriovenous shunt; flow load; vascular dilatation; angiography; pressure-volume relationship; transendothelial protein permeability

According to the review by Liebow (19), the significant effect of blood flow or flow-oriented stress on the growth of vessel caliber was initially pointed out by Thoma (1893), who observed in chicken embryos that the pathways of the fastest blood velocity became the main arteries while those with slower velocity atrophied. This effect, controlling the vessel diameter during angiogenesis, was clearly distinguished from that of the tangential stress due to the transmural pressure, which induced the changes in the wall thickness. Later studies on arteriovenous fistulas and on the collateral circulation (17, 19, 23, 26, 29) also show that increased blood flow induces blood vessel dilatation. Recent investigations on atherosclerosis (4, 5, 11, 13, 21, 24) suggest that a flow-oriented stress, i.e., the wall shear stress exerted by the adjacent flow velocity, might play a significant role not only on the pathogenesis of this disease but also on the physiological adaptation of the vascular wall. Fry and his colleagues (3, 10, 12, 15, 16) demonstrated that increased wall shear stress caused by increased flow velocity enhances protein permeability across the endothelial layer of the arterial wall; moderately elevated stress induces intimal hyperplasia of a physiological nature and moder ate increases in the arterial diameter, although excessive stress load causes erosion of the endothelium followed by histopathological changes resembling the early lesions of atherosclerosis.

If increases in shear stress really induce the adaptive vascular dilatation, one can assume an autoregulatory mechanism of wall shear as follows: the shear rate (γ) at the inner surface of the vessel wall is given by

\[ \gamma = (m + 2)f/(\pi r^2) \]  

and the wall shear stress (τ) by

\[ \tau = \eta \gamma \]  

where f is the total blood flow, r the internal radius of the vessel, and η the blood viscosity. The value of the dimensionless number m depends on the flow condition. For the laminar flow, m = 2 and for the turbulent flow, m > 2. In either case, wall shear stress, when increased during a sustained increase in blood flow, induces the adaptive enlargement of the vessel radius, which acts as a negative feedback to reduce the stress itself. If the wall shear stress fully controls the enlargement and reduction of the vessel diameter as hypothesized above, the stress will be maintained constant at the control level for any sustained blood flow changes. As discussed later, the autoregulatory mechanism can provide a reasonable basis to explain flow-radius relationships in the vascular system.

This study was performed to examine experimentally the hypothesis of constant shear stress regulation as stated above. An arteriovenous (a-v) shunt was constructed between the common carotid artery and the external jugular vein. These vessels were chosen because Flaherty et al. (10) observed only physiological responses to the increased flow load in the histology, contrary to the pathological changes in the iliofemoral a-v shunt. The adaptive changes in the shunted arterial radius and in the wall shear rate induced by the increased or decreased flow load was then analyzed quantitatively.

METHODS

Twenty-eight mongrel dogs (8-27 kg) were anesthetized with sodium pentobarbital (30 mg/kg). The ipsilateral common carotid artery and external jugular vein were exposed, and a side-to-side anastomosis was constructed between them at a rather high level. Both vasa-
cular walls were cut longitudinally in lengths varying from 5 to 20 mm, and the cut edges were sutured continuously to make an anastomosis with openings of various sizes. The contralateral artery and vein served as sham-operated controls. These vessels were exposed and the adventitia were sutured together at the same level of the neck as was done with the a-v shunt. The whole operation was performed under sterile conditions.

The animals were kept for three different periods: 12 dogs in chronic experiments for 6-8 mo; 4 in subacute experiments for 1 wk, and 6 in acute experiments for 3 days.

For the final measurements, the animals were anesthetized as before, and the carotid arteries of both sides were exposed. The blood flow rate through the artery was measured at a site proximal to the anastomosis by an electromagnetic flowmeter (Narco, RT500). Aortic pressure was measured with a catheter introduced via the femoral artery and connected to a strain gauge manometer (Statham, P231D). In the preliminary experiments, the pressure drop at the proximal part of the carotid artery was measured with a needle inserted into the artery distal to the anastomosis. The outputs of the flowmeter and manometers were recorded on a pen recorder (polygraph model 142-8, Sanei, Japan).

Arterial internal diameter was estimated in vivo by angiography in six chronic experiments. An aortic catheter was advanced into the left ventricle for injecting the contrast medium (Urographin, Sankyo, Japan). A small dental 3.2 X 4.1 cm X-ray film (DF-58, Kodak) was placed just behind the carotid artery (dorsal side) 3-4 cm proximal to the anastomosis, and X-ray was radiated from the ventral side for 0.1 ms during the indicator injection. Steel staples (commercially available paper fasteners) attached to the film cover were used as a scale marker (see Fig. 3). The two right-angle arms of the staples served to correct the measured vessel diameter for parallax, as shown in Fig. 1. The measurement was repeated 5-6 times for each animal.

In all experiments, the pressure-volume (P-V) relationship of the carotid artery was determined. The artery was occluded at two sites, one about 2-3 cm proximal to the anastomosis, and the other 4-5 cm further upstream toward the heart. Two hard Teflon catheters were cannulated at the occluded ends, one connected to the strain gauge manometer, and the other to an injection syringe. Care was taken to maintain the in situ length of the occluded segment, which was exactly measured with bow compasses. Before the P-V measurement was started, the content of the segment was extracted until the segment completely collapsed. The inflation was then started by successive injections of 0.05 or 0.1 ml of warm saline at 37°C from the syringe, and the stepwise change of the internal pressure was recorded on the polygraph. Every rapid injection was followed by a decline in pressure due to the stress-relaxation; therefore the next infusion was started when the preceding pressure reached a steady value. When the internal pressure reached or slightly exceeded the aortic pressure, the deflation process was initiated by withdrawing the same amount of the saline from the segment as had been injected during the inflation phase. It was continued until the segment completely collapsed. Such inflation-deflation cycles were repeated at least five times for each artery. From these P-V curves, pressure-radius (P-r) diagrams were obtained by calculating the internal radius r from the volume data V using \( r = \sqrt{V/(\pi L)} \) where L is the in situ length of the occluded segment.

In four chronic and six acute experiments, Evans blue dye (EBD or T-1824, 30 mg/kg) had been injected intravenously 3 days prior to the P-V measurements. The arterial segment of these animals was resected and stored in 10% formaldehyde solution. The segment was cut longitudinally, opened, and fastened on a board, endothelial surface upward, using pins. A pencil-type reflectometer (Fig. 2), especially designed for this study, was used to evaluate the EBD density in the sample. In this device, the light from a filament lamp was conducted by a glass-fiber bundle and was used to illuminate the sample. A cylindrical screen was placed around the probe to mask the stray light. The screen maintained a distance of 1 mm between the probe and the sample. The light reflected from the sample was conducted by another bundle to a CdS sensor (P201C, Hamamatsu TV, Japan), which was connected to an electronic bridge amplifier.

![Fig. 1. Estimation of internal diameter \( d \) of artery from width of vascular shadow \( d' \) on angiograms. Steel staple on the X-ray film, used primarily as a scale marker, was also utilized to correct estimation error due to X-ray parallax \( \theta \) because \( \theta \) is related to length of right-angled arm \( L \) and its shadow on the film \( L' \), as \( \theta = \tan^{-1}(L/L') \).](http://ajpheart.physiology.org/)

![Fig. 2. Schematic illustration of pencil-type reflectometer used to evaluate relative density of Evans blue dye in vascular wall (sec text).](http://ajpheart.physiology.org/)
The CdS cell was most sensitive to the light band of 650-700 nm, and its electric resistance decreased exponentially with the light intensity. The output voltage of the bridge circuit, which was proportional to the resistance change, was recorded on a pen recorder. The device was initially placed on a nonreflective black cloth to determine the base line. The endothelial surface of an unstained arterial surface, otherwise treated like the sample, served as a reference. The deflection of the unstained white artery (ΔW) and that of the stained artery (ΔS) from the base line were obtained, and the relative intensity of the absorbed light (a) was determined by $a = 1 - (ΔS/ΔW)$. The measurement was repeated at several spots on the sample surface.

RESULTS

Figure 3 shows two typical examples of the arterial angiography obtained in the chronic experiments. Figure 3A shows a moderate dilatation of the internal diameter of the artery subjected to the increased flow load. In contrast, a distinct attenuation of the diameter was observed in the shunted artery in Fig. 3B, in which the anastomosis was almost closed with blood clot, and the blood flow was less than 10% of the control at the time of the measurement. The radial width of the vascular shadow was measured at several sites along each artery. The mean width was then calibrated with the scale marker and was corrected for the X-ray radiation angle.
as shown in Fig. 1. However, several sheets of the film were discarded because the X-ray angle of incidence was quite oblique and the outline of the vascular contour was very vague. The obtained diameters showed slight variations from sheet to sheet mainly due to the pulse pressure. To minimize such an effect, the arterial diameter was estimated by taking the average value again.

The P-r relationships of the control and shunted carotid arteries from 16 experiments are summarized in Fig. 4, upper panel and lower panel, respectively. In these figures, the abscissa indicates the radius normalized to the cube root of the body weight. The curves showed hysteresis at each inflation-deflation cycle and a gradual shift in the hysteresis in subsequent cycles, probably due to contraction of the vascular smooth muscle, as demonstrated by Cox (6, 7). After several cycles, however, the hysteresis and its shift decreased gradually, and the curve had a tendency to stabilize. In the majority of the measurements, no significant shift was observed after the fifth cycle. The shunted arteries had essentially the same course as the controls but with slightly higher mean values and greater standard deviations due to the adaptive responses.

When carotid arterial pressure was measured by needle puncture in six dogs during the preliminary experiments, the pressure drop from the aortic arch to the common carotid artery just proximal to the anastomosis was only 1.5 ± 0.9 mmHg for the control arteries and 3.7 ± 1.8 for the shunted arteries. Such a small pressure difference would probably yield no significant error in estimation of the radius in the physiological range of arterial pressure where the arterial wall was less distensible, as seen in Fig. 4. Thus, the aortic pressure could be used as the mean distending pressure of the proximal carotid artery to estimate the internal radius at the prevailing pressure during flow measurement.

From every curve of the P-r diagram, the radii corresponding to the aortic pressure were determined and compared with the in vivo data acquired by angiography. The data obtained from the inflation slope of the fifth cycle showed the highest correlation with the in vivo data (Fig. 5). The correlation coefficient was 0.973 and errors were around 10%. Therefore the arterial radius was finally obtained from the arithmetic mean of the data for the slope of the fifth inflation curve and that from the angiography, if both were available.

Using the internal radius (r) thus determined and the mean blood flow rate (f), we calculated the wall shear rate from Eq. 1, assuming the flow to be laminar (m = 2). This assumption is justified because Reynolds numbers (Re) calculated from Re = 2pf/(mηr); η being the density of blood (1.03 ml⁻¹) and η being the blood viscosity in dogs [3 × 10⁻² poise (P)], were all less than 1,000, i.e., far below than the critical level of 2,000 for the turbulent flow through a smooth straight tube. Nevertheless, in the majority of experiments a harsh thrill was
palpable at the a-v shunt. Strong turbulence of flow through the shunt opening was suspected. To examine the retrograde influence of this turbulent vortex, the radial component of flow proximal to the fistula was quite large at the shunt opening, it diminished very sharply as the probe was moved away from the opening. At a point 3 cm proximal to the anastomosis, the radial component decreased to approximately 15% of the maximum even during flow rates as high as 25-35 ml/min kg body wt\(^{-1}\) (about 3-4 times of the control flow). At the point 3 cm upstream, it became comparable with the control artery where no turbulence was expected from Re value of 150-200. These observations show that flow was laminar at distances greater than 2-3 cm proximal to the anastomosis and that this location was suitable for radius measurement. The statistical summary of the measured and calculated data is listed in Table 1.

As seen in Fig. 6, the radius of the shunted artery \(r_s\) in the acute or subacute experiments was approximately the same as the control radius \(r_c\). The differences in the wall shear rate between the paired arteries were almost proportional to the differences in the flow rate. After 6-8 mo adaptation, however, substantial changes were observed in \(r_s\), which varied according to the flow rate. The shunted flow rate \(f_s\), which was larger than the control flow rate \(f_c\), was associated with the larger arterial radius and vice versa. Such radius changes were quite effective in reducing the shear rate difference between the paired arteries.

To show the compensatory effect of the adaptive radius changes, the wall shear rate ratio \((\gamma_s/\gamma_c)\) was plotted against the blood flow ratio \(f_s/f_c\) as shown in Fig. 7. The broken line indicates the initial condition, with no adaptive regulation, in which the paired arterial radii were equal; the thin solid line indicates the condition of complete regulation in which the shear rates of the paired arteries were equal. The data points of the acute experiments fell on the line of no regulation. Some of the data points from the subacute experiments were slightly shifted from the initial level, implying that the adaptive response had probably started within 1 wk. The data points of the chronic experiments were all shifted far away from the initial level and clustered rather close to the line of complete regulation. In 9 of 12 experiments in which the shunted flow rate was less than four times the control flow rate, the shear ratios were all between 1.0 and 1.15, implying that the regulation of the shear rate at such moderate flow load had been completed in the 6- to 8-mo period. This result is quite consistent with the proposed hypothesis of the constant shear stress regulation. In three arteries subjected to the greatest flow load \((f_s/f_c > 4)\), the shear rate remained 2-3 times larger than the control, suggesting an incomplete regulatory response to this extreme stress.

The results of the reflectometry of EBD-stained arteries are shown in Fig. 8. The ratio of the absorbed red light between the paired arteries correlated well with the

![TABLE 1. Statistical summary of the measured and calculated data](http://ajpheart.physiology.org/)

<table>
<thead>
<tr>
<th>Aortic Pressure, mmHg</th>
<th>Blood Flow Rate, ml min(^{-1}) kg(^{-1})</th>
<th>Internal Radius, mm kg(^{-1})(^{1/3})</th>
<th>Wall Shear Rate, s(^{-1})</th>
<th>Reynolds Number</th>
<th>Relative Light Absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blood flow rate (shunted/control)</td>
<td>Internal radius (shunted/control)</td>
<td>Wall shear rate (shunted/control)</td>
<td>Reynolds number (shunted/control)</td>
<td>Relative light absorption (shunted/control)</td>
</tr>
<tr>
<td></td>
<td>(f_s/f_c)</td>
<td>(r_s/r_c)</td>
<td>(\gamma_s/\gamma_c)</td>
<td>(Re_s/Re_c)</td>
<td>(a_s/a_c)</td>
</tr>
<tr>
<td><strong>Chronic experiments</strong> (6-8 mo, (n=12))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>113</td>
<td>7.6</td>
<td>20.8</td>
<td>2.83</td>
<td>0.872</td>
<td>0.773</td>
</tr>
<tr>
<td>±32</td>
<td>±2.3</td>
<td>±18.0</td>
<td>±2.53</td>
<td>±0.042</td>
<td>±0.223</td>
</tr>
<tr>
<td><strong>Subacute experiments</strong> (1 wk, (n=4))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>114</td>
<td>5.5</td>
<td>15.1</td>
<td>2.62</td>
<td>0.640</td>
<td>0.668</td>
</tr>
<tr>
<td>±26</td>
<td>±1.3</td>
<td>±14.6</td>
<td>±2.31</td>
<td>±0.041</td>
<td>±0.072</td>
</tr>
<tr>
<td><strong>Acute experiments</strong> (3 days, (n=6))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95</td>
<td>8.8</td>
<td>14.8</td>
<td>1.68</td>
<td>0.675</td>
<td>0.679</td>
</tr>
<tr>
<td>+11</td>
<td>+1.8</td>
<td>+6.4</td>
<td>+0.80</td>
<td>+0.097</td>
<td>+0.083</td>
</tr>
</tbody>
</table>

All values are means \(+\ SD\).
ADAPTIVE WALL SHEAR STRESS REGULATION

The experimental determination of the arterial wall shear stress required careful measurement of the internal diameter. We employed two entirely different methods, in vivo angiography and in vitro pressure-volume relationships. Although neither may be adequate when used alone, the mutual check between the independently obtained data served to improve the reliability of the diameter estimation in this study. The close correlation between the in vivo data and the in vitro observations after the fifth inflation suggested a rather low myogenic tone of this artery during the measurements.

The data of measured radius showed chronic adaptive changes related to the flow rate, i.e., dilatation for an increased flow load and atrophy for a decreased flow load (Fig. 6). These results agreed with those by Flaherty et al. (10) reporting moderate arterial dilatation of carotid and iliofemoral a-v shunts in dogs. Since the adaptive response in our study was evaluated as the relative change with respect to the control artery, only hemodynamic causes could be attributed to these changes. The hormonal or metabolic factors known to induce adaptive vascular responses (19) could have little influence on these results because they would be equally effective on the shunted and the control arteries. The tangential tension (or stress) could also be eliminated from the causal stress because at arterial flows on the shunted side, which were larger than the control, the internal pressure was always lower than the control. Although the difference was slight, the lower tension or stress could hardly be the initiating factor of the vascular dilatation.

The pulse pressure of the shunted artery was also less than that of the control. The longitudinal tension along the artery, which was slightly increased by construction of the anastomosis, was made approximately equal to that of the control artery by the sham operation. Turbulent flow could not be the main cause of this adaptation because the turbulent area was avoided in the measurements. Moreover, atrophy of the artery in response to a decreased flow rate was observed in two chronic experiments (Fig. 6), which in no case was caused by the turbulent flow.

Because the most striking difference in the hemodynamic factors of the paired arteries was blood flow rate, it was quite likely that flow-oriented stress was the major cause of the vascular adaptive responses. The calculated wall shear rates in the chronic experiments showed almost complete regulation of the stress, as shown in Fig. 7. The shear rate differences were within 15%, even though the flow load varied four times as much as the control level. This result itself strongly suggests that the wall shear stress was the predominant factor in initiating and controlling the adaptive response.

There are several lines of evidence from vascular morphometry, blood rheology, and clinical hematology supporting the hypothesis of constant shear stress regulation. Increased blood viscosity in such hematologic diseases as polycythemia vera, Waldenström's macroglobulinemia, and sickle cell anemia is clinically known to be associated with dilatation of the peripheral vessels (8, 22). The typical vascular signs of these diseases are

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**FIG. 7.** Regulation of wall shear rate by adaptive changes in arterial radius. Shear rates were calculated by Eq. 1 with common data in Fig. 6. Shear rate ratio (shunted/control) in acute experiments (a) are all on the line of no regulation ($r = 1$; $f_s/f_c$), but those of the subacute experiments (m) are slightly separated from it. Chronic data (c) are very near to the line of complete regulation ($r = 1$), except those corresponding to the very great flow loads ($f_s/f_c > 4$).

**FIG. 8.** Result of reflectrometry for the EBD-stained arteries. Relative intensity of light absorption (shunted/control) indicates changes in the EBD density in the vascular wall. Note that EBD-bound serum protein permeability depends on wall shear stress.

**DISCUSSION**

ratio of the wall shear rate. The correlation coefficient was 0.934. This result indicated that the transendothelial uptake of EBD-bound protein was increased as the wall shear rate (or stress) increased. It was also found that EBD concentrations of the chronically adapted arteries were similar to that in the controls, because the wall shear rates had been regulated at a value almost equal to the control level, even though the flow ratio varied very significantly, ranging from 0.04 to 2.0.
observed in the ocular fundus, i.e., engorgement, dilatation, and tortuosity of the veins and sometimes of the arteries (18, 25). Although increased blood viscosity may be associated with a decrease in blood flow, it would nevertheless yield higher wall shear stress, as indicated by Eq. 2. This vascular dilatation may be considered as an adaptive response to the increased shear stress.

One of the morphological characteristics of the vascular tree is that with few exceptions, the cross-sectional area of the mother branch is less than the sum of cross-sectional areas of the daughter branches; the relation between the radii of the mother and daughter branches \((r_0, r_1, \text{and } r_2)\) is formulated as

\[ r_0^n = r_1^n + r_2^n \]  

where \(n\) is greater than 2. Moreover, for blood flow at these branches

\[ f_0 = f_1 + f_2 \]  

Equations 3 and 4 imply that

\[ f/r^n = \text{constant} \]  

The proposed hypothesis expressed by Eqs. 1 and 2 holds if \(n = 3\). Radius measurements, using casts of the branches, have been performed in the systemic arterial tree by Groat (16) and in the renal and mesenteric arterial trees by Suwa and Takahashi (28). The statistically obtained value of \(n\) was 2.6 for the former and 2.7 for the latter, very nearly 3. The general characteristics of the flow-radius relationship in the arterial trees can be largely explained by the autoregulatory mechanism of the wall shear.

The mean wall shear rate at the control carotid artery in this study was 525 s\(^{-1}\) (Table 1). Withamore (30) gave a similar estimate (600 s\(^{-1}\)) for the large arteries in dogs having comparable diameters of 0.5 cm. Using an apparent blood viscosity of \(3 \times 10^{-3}\) \(\text{Poise}\) to these estimates give a wall shear stress of 15-20 dyn/cm\(^2\). He also estimated that the blood velocity at terminal arterial branches having a diameter of 0.06 cm is 6 cm/s and of arterioles having a diameter of 0.002 cm is 0.3 cm/s. For each estimate, we obtain wall shear rates of 800 and 1,200 s\(^{-1}\) and wall shear stresses of 22 and 14 dyn/cm\(^2\), respectively, by taking into account the Fahraeus-Lindqvist effect in the vessels of such sizes. In addition, we obtain similar estimates for the capillary bed from the measurement of the pressure gradient. For the capillary wall, which is always in contact with and impinged upon by red cells, Eq. 1 is obviously unsuitable for calculation of wall shear. Instead, Lipowsky and Zweifach (20) estimated the wall shear stress at the capillary network in the cat mesentery from the pressure gradient along the capillary channel \((\Delta \text{P}/L)\), directly measured with a micropipette and the capillary diameter \(d\), using the relation

\[ \tau = (\Delta \text{P}/L)(d/4) \]  

Their conclusion was that the capillary wall shear stress \(\tau\) should be of the order of 10 dyn/cm\(^2\) in vivo. In the capillary bed of the rat cremaster muscle, Smaje, Zweifach, and Intaglietta (27) measured a pressure drop \(\Delta \text{P}\) of 7 mmHg along a capillary length \(L\) of 615 \(\mu\)m. In rat tenuissimus muscle capillaries, Eriksson and Myrhage (9) reported a \(\Delta \text{P}\) of 15 mmHg along an \(L\) of 1,015 \(\mu\)m. Substituting these pressure gradients and a capillary diameter of 4.1 \(\mu\)m as measured by Baez (1) into Eq. 5, we estimate shear stresses of 15-20 dyn/cm\(^2\). These similar estimates suggest that wall shear stress in the entire arterial tree and its capillary beds is controlled at an approximately constant level, probably by the same autoregulatory mechanism.

These morphological and rheological facts described above, as well as the experimental results in this study are all consistent with the hypothesis of constant shear stress regulation. Although the mechanism of this adaptive response is not yet clear, protein turnover in the wall as controlled by endothelial shear stress might be related to it. Fry (13) and Fry et al. (15) demonstrated that an increase in the wall shear caused increased protein permeability of the endothelial cell layer. In vitro experiments by Carew (2) showed that protein flux increased in proportion to the second power of the shear stress. The findings in the present study are consistent with these results. As shown in Fig. 8, we found a close correlation between the wall shear and FMD staining, although we did not analyze the transported mass of dye quantitatively from the reflected light intensity as Fry et al. (14, 15) did. It was also evident from many studies that sustained high wall shear is associated with intimal hyperplasia (10,12) and, to a certain extent, with dilatation of the vascular lumen (17, 23, 26, 29); our observations are consistent with these findings. Therefore, if increased protein permeability or resultant protein accumulation really induces vascular hyperplasia or dilatation, the autoregulatory response presented here is reasonably well explained. However, experimental evidence is still lacking to further delineate the mechanism of these adaptive responses.

A few arteries chronically subjected to shunt flow greater than four times control did not show complete regulation of the wall shear. Several possible reasons can be given for this incomplete regulation. It might be due to the inherent limitation of the adaptive capacity of large arteries. Alternatively, the adaptive responses to such great stresses might require longer than the 6-8 mo over which our observations extended. It is also likely that some pathological changes might be induced by such extreme stresses and these may disturb the physiological adaptation.

We thank Prof. Juro Iriuchijima, Prof. Hideyuki Isogai, Prof. Razaq Bukhari, and Dr. Setsuo Takatani for their many helpful comments, and Mr. Kenichi Yamakoshi and Mr. Hideaki Shimazu for their skillful assistance.

This work was partly supported by the research fund from Japan Research Promotion Society for Cardiovascular Diseases in 1978 and 1979.

Received 3 August 1979; accepted in final form 20 February 1980.

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