Hemodynamics and Wall Shear Rate in the Abdominal Aorta of Dogs
Effects of Vasoactive Agents

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Abstract Vasoactive drugs are known to affect impedance (pressure/flow) and vessel wall motion in arteries. The nonlinear theory of oscillatory flow in straight elastic vessels indicates that wall shear rate is affected by changes in impedance phase angle and wall motion. To test whether wall shear rate depends on impedance phase angle and wall motion in vivo, wall shear rate was measured in the abdominal aorta of anesthetized dogs by using a flush-mounted hot-film anemometer, and the hemodynamic state was characterized by pressure, flow, and vessel dimension measurements. Vasoconstrictors (nitroprusside and isoproterenol) and vasoconstrictors (angiotensin II and norepinephrine) were administered acutely, and the responses of wall shear rate and hemodynamics were determined. In the control state (no drugs), peak wall shear rate was 1835±153 s⁻¹ (mean±SEM). The vasodilators induced large increases in impedance phase angle and wall motion concomitant with large increases in peak wall shear rate (62.4±20.4% for nitroprusside and 68.9±28.3% for isoproterenol), which were not predicted accurately by Womersley's theory of oscillatory flow in a rigid vessel or the nonlinear theory of oscillatory flow in an elastic vessel, with measured flow and vessel dimension used as inputs. The vasoconstrictors induced small decreases in impedance phase angle and wall motion and small changes in peak wall shear rate (increase, 30.5±8.0% for norepinephrine; decrease, 18.2±7.1% for angiotensin II), which were predicted accurately by Womersley's theory. The present study shows that vasoactive drugs, particularly vasodilators, can have significant effects on wall shear rate (stress) in the abdominal aorta that appear to be related to changes in impedance phase angle and vessel wall motion. However, the effects on wall shear rate are not predicted accurately by straight-tube theory. (Circ Res. 1994;75:637-649.)

Key Words • wall shear rate • impedance • vasodilators • vasoconstrictors

The two basic mechanical forces (per unit area) imposed by blood on arterial walls are pressure and wall shear stress (WSS). Pressure is a familiar force, which acts perpendicular to the axis of the blood vessel wall, whereas WSS, which is less familiar, acts parallel to the wall and is defined as

(1) \[ \text{WSS} = \frac{dv}{dr} \bigg|_{r=a} = \mu S \]

where \( \mu \) is the fluid viscosity, \( \frac{dv}{dr} \bigg|_{r=a} \) is the wall shear rate (S), \( v \) is the axial velocity, \( r \) is the radial coordinate, and \( a \) is the tube radius. Blood pressure is easily measured and routinely used to characterize the state of the cardiovascular system in health and disease. The response of blood pressure to vasoactive drugs is well documented. On the other hand, WSS is difficult to measure directly in vivo and is therefore rarely used to characterize hemodynamic status. To our knowledge, the response of WSS to vasoactive drugs is unknown.

It has been demonstrated that WSS has a significant influence on the production of biochemicals by endothelial cells, the permeability of the endothelial layer to macromolecules and water, and the regulation of arterial internal diameter. In addition, the role of WSS as a localizing factor in atherosclerosis has been debated for many years. WSS has been estimated accurately in vitro by using high-resolution near-wall velocity profile measurements obtained by laser Doppler anemometry (LDA) in transparent arterial casts with clear blood analogue fluids. However, this method has not been applied to arteries in vivo because of optical limitations. Techniques that can be applied noninvasively for blood velocity imaging, such as Doppler ultrasound and magnetic resonance imaging, have sample volumes that are two to three orders of magnitude larger than those provided by LDA and are thus not well suited to quantitative WSS measurements in vivo. The only technique that has been applied successfully for in vivo wall shear measurements is flush-mounted hot-film anemometry (FMHFA). In this invasive technique, a small electrically heated platinum wire is mounted flush on the inner wall of the blood vessel, and the heat loss, which is related to the wall shear rate, is measured. Ling et al. and Miller and Hollis used FMHFA to measure WSS in the thoracic aorta of open-chested dogs, and they obtained consistent results for the peak WSS in the range of 100 to 200 dyne/cm². Our group has considerable experience in the application of FMHFA to wall shear rate measurements in physiological flows in vitro, as reviewed by Klangchar et al. In the present study, we measured wall shear rate in the abdominal aorta of dogs by using FMHFA. Pres-
sure, flow, and vessel diameter were also measured to provide a characterization of the hemodynamic state, and several vasoactive drugs were administered to alter the hemodynamic state. The nonlinear theory of oscillatory flow in straight elastic tubes indicates that wall shear rate depends on the phase angle of the impedance (pressure/flow) and the wall vessel diameter variation over a cycle. The present study allows us to test whether such relations hold in vivo. The abdominal aorta was chosen for study for several reasons: (1) It is a relatively straight section of vessel that is amenable to theoretical analysis. (2) It has a large enough diameter for application of FMHFA. (3) It is below the diaphragm, so a respirator is not required. The FMHFA measurements were used to address the following basic physiological questions: (1) What is the wall shear rate (stress) level in the abdominal aorta? (2) How does wall shear rate respond to vasoactive drugs that alter impedance and vessel wall motion?

### Materials and Methods

#### Surgical Procedure and Instrument Placement

Eight female dogs with an average weight of 21.9±3.1 kg (mean±1 SD) were used. Animals were premedicated with 2.5 mL atropine (1.25 mg per dog), and anesthesia was induced with pentobarbital sodium (20 to 30 mg/kg). An endotracheal tube was introduced, and a RET-1 copper constantan thermocouple attached to a rectal thermometer readout (model BAT 8, Bailey Instruments) was inserted. Anesthesia was maintained with a 1% to 2% halothane/oxygen mixture. A midline abdominal incision was made from the xiphisternum to the pubis, and the abdominal walls were held apart with a retractor. The abdominal aorta was bluntly dissected free of the surrounding tissues from the renal arteries to the aortic bifurcation. In the region ≈5 cm anterior to the ovarian artery, the small side arteries were double-ligated and transected. Four different transducers were placed on this portion of the aorta. Fig 1 is a schematic diagram showing the approximate locations of the transducers.

Two circular disk ultrasonic vessel diameter transducer crystals of 2.5-mm diameter (Triton Technologies, Inc) were placed on opposite sides of the aorta ≈2 cm caudal to the renal arteries. The crystals were first glued to polyester fabric patches, and these were sewn to the aortic wall with 6-0 braided silk after ensuring parallel alignment. The dimension crystals were interfaced to a four-channel Sonomicrometer (model 120-1001-12, Triton Technology, Inc) with a flat frequency response to 100 Hz. Based on comparison with direct caliper measurements, the accuracy of the sonomicrometer output was estimated to be ±0.5 mm. This error was due to slight off-diameter crystal placement and not inaccuracy of the instrument.

Next, a tunnel was made under the abdominal aorta, immediately caudal to the ovarian arteries, and the bottom U-bracket of a 10-mm ultrasonic flow probe (No. 10S probe, Transonic Systems, Inc) was inserted. The probe body was then screwed in place on the U-bracket. The ultrasonic flow probe did not require physical contact with the artery wall to measure flow (acoustic gel was applied); therefore, the flow probe did not interfere with the radial pulsations of the aorta. The ultrasonic flowmeter (model T101, Transonic Systems, Inc) was operated at the 30-Hz filter setting of the instrument. This introduced an 8-millisecond time delay in the flow signal, which was accounted for in subsequent data processing, but there was no alteration of the flow amplitude. The accuracy of the flowmeter output was determined by a stopwatch and bucket method after each experiment by using an excised portion of the thoracic aorta and the animal’s blood run through a flow loop (see hot-film anemometer calibration section). The error was usually <±5% and always <±10%.

A 2.5-cm cutdown on the medial thigh exposed the right femoral artery for insertion of a catheter-tipped pressure transducer (No. 5F, Millar Instruments), which was advanced to the bifurcation of the iliac arteries. The location of the tip of the catheter was checked by palpating the aorta. The pressure transducer was controlled by a model TCB-500 transducer control unit (Millar Instruments). To minimize baseline drift, the catheter was soaked in a 37°C water bath for 1 hour before insertion. This instrument has a uniform frequency response to 10 kHz. The internal electrical calibration was checked with an electronic pressure calibration, and the deviation was always <±5%. The manual calibration was used to convert the transducer output signal.

The adventitia was then stripped away from the site where the FMHFA probe was to be inserted, midway between the ovarian and renal arteries on the ventral surface of the aorta. Heparin (3000 U) was administered 10 minutes before the probe insertion to prevent clotting on the probe surface. The aorta was then clamped just distal to the dimension crystals and just proximal to the flowmeter bracket with bowel clamps. A purse-string suture of 6-0 braided silk was sewn into the muscularis around the site of the hole for the hot-film probe before making the hole. A slit was made either with a 19-gauge butterfly needle (two experiments) or a microscalpel with a diamond-shaped tip. The microscalpel was superior because the thin tip seemed to prevent tearing of the artery at the incision commissures. A schematic of the special FMHFA probe design (model 1237D, TSI, Inc) used in these experiments is shown in Fig 2. The active element of the probe is a 0.80×0.125-mm platinum film covered by a thin quartz substrate coating, which acts to insulate the electric circuitry. This is surrounded by a protective stainless-steel jacket, leaving only the tip exposed. The jacket is cold-rolled at the sensor end, forming a flange, which is ≈0.05 mm in thickness. The outside diameter of the probe shaft is 0.90 mm, and the probe tip, including the flange, has an outside diameter of 1.37 mm. A movable Teflon collar is mated to the flange. The basic operation of the FMHFA is quite simple in principle. The platinum film serves as one arm of a Wheatstone bridge (IFA model 100, TSI, Inc) and is maintained at a constant temperature (=5°C above ambient) by the bridge circuit. Because the film is maintained at constant temperature, the film current (or bridge voltage [E]), which provides joule heating of the film, is

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**Fig 1. Schematic diagram of the abdominal aorta showing the approximate placement of experimental probes.**
Zenith 386 personal computer. All four variables (pressure, flow rate, diameter, and hot-film anemometer voltage) were sampled every 3 milliseconds. Data files taken during nitroprusside and angiotensin infusion were tight for 2 seconds, and then an additional two to four data files including the hot-film anemometer output were taken during the control state (before drugs). Drugs (described below) were then administered in a random order. Aortic pressure was monitored to determine when a new hemodynamic steady state was established, and then four to two data files, including all signals, were gathered. A recovery period of between 10 to 40 minutes (nitroprusside) was required for the animal’s hemodynamics to return to the control level. After return to the control state, another drug was administered, and the measurement sequence was repeated.

**Vasoactive Drugs**

Four vasoactive drugs were prepared. Sodium nitroprusside was obtained in powder form and dissolved in isotonic saline to give a 0.1-mg/mL solution. The solution was administered as an intravenous drip at ~6.0 to 12.0 mL/min. Norepinephrine was purchased as a 1.0-mg/mL solution, and 0.03 to 0.04 mL was administered through the intravenous line as a bolus. Isoproterenol was obtained as a .02-mg/mL solution, and 4.0 mL was injected through the intravenous line as a bolus. Angiotensin was purchased as a 2.0-mg/mL solution; 1.0 mL of this solution was added to 100 mL of 5% dextrose/sodium chloride solution, and 1.0 to 2.0 mL of solution was administered in 1.0 minute as a drip through the intravenous line.

At the end of each experiment, a small sample of venous blood was collected for hematocrit measurement, and then euthanasia was usually accomplished by exsanguination because the blood was required for calibration of the hot-film probe. If exsanguination was not complete, an injection of pentobarbital was used to ensure cardiac arrest.

**Determination of Wall Shear Rate**

The standard calibration equation relating FMHFA bridge voltage ($E_b$) to wall shear rate ($S$) is as follows\(^8\):

$$E_b^2 = A + B S^{1/3}$$

The constants $A$ and $B$ were determined by steady flow calibration in the Poiseuille flow loop described below.

The calibration loop consisted of a constant-temperature water bath, a roller pump, an electromagnetic flowmeter, the excised and cannulated thoracic aorta, and the exsanguinated blood. Approximately 1 L of the animal’s blood was collected into sodium citrate vacuum bottles after completion of the in vivo experiment. The excised thoracic aorta was cleaned of surrounding tissue, and all intercostal arteries were ligated. The aorta was fitted onto glass cannulas, reextented to its in vivo length, and inserted into the flow loop. The upstream cannula was long enough to ensure fully developed laminar flow (Poiseuille flow) at a maximum Reynolds number of 2000. The diameter of the glass cannulas and the approximate diameter of the thoracic aorta were 8 mm. The upstream cannula was 50 cm long, and the FMHFA probe was positioned 4 to 6 cm downstream from the cannula/thoracic aorta junction. The temperature for each calibration procedure was set at the temperature indicated by the rectal thermometer during the in vivo experiment. For insertion of the hot-film probe, a slit was made in the excised aorta that was similar to that of the in vivo experiment, and the hot-film anemometer probe was inserted and flush-mounted. During each calibration run, the flow was started at either the low or the high end of the flow-rate range, and four or five data points were gathered while increasing (or decreasing) the flow, and then

**Data Collection and Measurement Sequence**

Data were collected with a model 500 Keithly System 16-bit A/D board (Keithly Metabyte/Asyst/DAC) integrated with a hot-film anemometer and a microcomputer. Data were collected at a rate of 60,000 samples per second, and each record was 60 seconds long (approximately 2000 data points).

A/D board values were stable; data files were taken before suture was tied tightly, and then an additional two to four data files including the hot-film anemometer output were taken during the control state (before drugs). Drugs (described below) were then administered in a random order. Aortic pressure was monitored to determine when a new hemodynamic steady state was established, and then two to four data files, including all signals, were gathered. A recovery period of between 10 to 40 minutes (nitroprusside) was required for the animal’s hemodynamics to return to the control level. After return to the control state, another drug was administered, and the measurement sequence was repeated.

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the flow rate was reversed for four to five additional data points. The flow rate ranged from nearly zero up to 2 L/min, the maximum flow rate attainable in laminar flow. This range was adequate for calibration of the probe, because in vivo flow rates at peak systole did not exceed 2 L/min during the administration of norepinephrine.

In Poiseuille flow (parabolic velocity profile), the wall shear rate, S, can be calculated as follows:

\[ S = \frac{4Q}{\pi R^3} \]

where \( Q \) is the volumetric flow rate and \( R \) is the radius. Flow rate \( Q \) was measured with the electromagnetic flowmeter (model 501, Carolina Medical). Radius \( R \) was obtained by subtracting the wall thickness from caliper readings of the outside diameter of the thoracic aorta while it was in the calibration flow loop. The wall thickness was estimated to be 0.6 mm on the basis of caliper measurement of a portion of the aorta that had been reextended to in vivo strains in both the longitudinal and circumferential directions. During calibration, flow rate \( Q \), vessel radius \( R \), and anemometer \( E_s \) were measured; shear rate \( S \) was calculated from Equation 2; and the constants A and B of Equation 2 were determined through linear regression of \( E_s^2 \) versus \( S^3 \).

Although the constants A and B were determined in Poiseuille flow, Equation 2 can be applied to any flow in which the thermal boundary layer on the hot-film probe surface is thin compared with the velocity boundary layer. Under such circumstances, the velocity profile within the thermal boundary layer can be approximated by the linear relationship \( U = SY \), where \( U \) is the axial velocity, \( Y \) is the perpendicular distance from the wall, and \( S \) is the wall shear rate. It is shown elsewhere that the thickness of the thermal boundary \( \delta_t \) is given by \( \delta_t = 1.24(L_D/\nu)^{1/3} \), where \( L \) is the dimension of the hot film in the flow direction (0.125 mm) and \( D_t \) is the thermal diffusivity of the fluid medium (1.4x10^{-7} cm²/s for water at 37°C). For a wall shear rate of 1000 s⁻¹ (order of magnitude of peak wall shear rates measured in the aorta), we estimate \( \delta_t = 0.032 \) mm. The thinnest anticipated velocity boundary layer \( \delta_t \) in the aorta would be the Stokes oscillatory boundary layer, with thickness \( \delta_t = 4\sqrt{\nu/\omega} \), where \( \nu \) is the kinematic viscosity (viscosity/density) and \( \omega \) is the angular frequency. Taking \( \nu = 7 \times 10^{-5} \) cm²/s (water at 37°C) and \( \omega = 30 \) radian/s (highest heart rate observed), we find \( \delta_t = 0.61 \) mm. Since \( \delta_t < \delta_t \), the constants A and B determined in Poiseuille flow should apply.

Application of Equation 2 to unsteady physiological flow depends on the dynamic response of the probe. Anemometer bridge “turn-on” experiments (Appendix) indicate a response time of 25 milliseconds for the probe used in these studies, suggesting that peak wall shear rates determined by Equation 2 at physiological frequencies in the dog (2-Hz fundamental frequency) would be attenuated somewhat because several harmonics are required to reproduce peak shear rates. Nandy and Tarbell18 showed that the application of Equation 2 to physiological pulsatile flows resulted in a prediction of peak wall shear rates with an accuracy of 14% by using the same type of probe as used in the present study. To compensate for the somewhat limited frequency response, the following dynamic model of the FMHFA has been used21:

\[ S = \frac{1}{B^3} \left( E_s^2 - A \right)^3 + \frac{d(E_s^2 - A)}{dt} \]

When the time derivative term in Equation 4 is small (slowly varying flows), Equation 2 is recovered. The dynamic parameter C is determined from bridge turn-on experiments described in the Appendix.

Fourier Analysis

Pressure, flow, and radius waveforms were Fourier-analyzed by using a 20 fast Fourier transform algorithm available in the ASYST package. The number of data points per beat varied from 100 to 200, and these were reduced to 64 evenly spaced points per beat following Fourier transformation, resulting in an equivalent data collection rate of 100 to 200 Hz. Between 8 and 25 beats were analyzed for each hemodynamic state, and Fourier coefficients were averaged.

The individual waveform spectra were then used to compute impedance (\( Z_0 \)) and pressure-strain (or viscoelastic modulus \( E_p \)) spectra for each hemodynamic state where

\[ Z_n = -\frac{P_n}{Q_n} = |Z_n|e^{i\theta_n} \]

and

\[ E_p = \frac{RP_n}{Q_n} = |E_p|e^{i\phi_n} \]

In the above, \( P_n \), \( Q_n \), and \( R \) are the complex Fourier coefficients of the nth harmonic of the pressure, flow, and outside-radius waveforms, respectively, and \( R \) is the mean outside radius. Spectra (\( Z_n \) and \( E_p \)) from different animal experiments were averaged to obtain composite spectra characterizing each hemodynamic state.

Wall Shear Rate From Womersley's Theory

The simplest theory available for predicting wall shear rate that takes into account the pulsatility of the physiological flow is Womersley’s theory.22 Given the Fourier coefficients for the flow waveform (\( Q_n \)), the wall shear rate is calculated from

\[ S = \sum_{n=0}^{\infty} \frac{-Q_n}{\pi R_n^3} \left[ \frac{X_n J_1(X_n)}{X_n J_0(X_n)} - 2 J_1(X_n) \right] \]

where

\[ X_n = \alpha_n \sqrt{\nu} \]

and

\[ \alpha_n = \frac{\bar R \sqrt{n \omega / \nu}}{\alpha_0} \]

In Equations 7 through 9, \( J_1 \) and \( J_0 \) are Bessel functions of the first kind, order zero and one, respectively; \( \bar R \) is the mean inside radius; \( \nu \) is the kinematic viscosity (viscosity/density); \( \alpha_0 \) is the unsteadiness parameter of the nth harmonic; and \( \omega \) is the fundamental angular frequency. The viscosity is taken as 0.038 poise following a correlation of Schneck23 for dog’s blood at 46% hematocrit and 37°C. The density of blood is estimated to be 1.08 g/cm³. The frequency, inside radius, and flow coefficients are determined from direct measurements on individual dogs.

Results

Representative flow, pressure, wall shear rate (without frequency response correction), and diameter waveforms for the control state and four drug-induced states, all from the same animal, are displayed in Figs 3 through 7. In the control state, the peak flow rate ranged from 0.8 to 1.2 L/min, and there was a noticeable diastolic flow pulse. The typical pressure pulse was 110/60 mm Hg with a mean pressure of 80 mm Hg. Normal diameter variations were 3% to 4% [(maximum−minimum)/mean], and the mean diameter was 6 to 7 mm. Wall shear rate waveforms show a large characteristic positive peak that is associated with systolic flow, and in some cases a smaller secondary peak.
that is associated with retrograde flow during diastole (eg, Fig 4) or associated with a secondary positive flow pulse during diastole (eg, Fig 7). Because the FMHFA measures heat loss from the film, it cannot distinguish flow (shear) direction; therefore, both forward (positive) and retrograde (negative) shear rates are recorded as positive.\textsuperscript{18} Peak wall shear rate without frequency-response correction was 1100 to 1400 s\textsuperscript{-1} (1600 to 2000 s\textsuperscript{-1} with frequency-response correction as described in the Appendix). Since there is some ambiguity concerning the proper sign (+ or −) for the shear rate during diastole, time-averaged (mean) values cannot be computed reliably. The fundamental frequency in the control state was ≈2 Hz.

Nitroprusside infusion (Fig 4) had little effect on flow rate magnitude or pulse frequency but did lead to a reduction in the diastolic flow level. Mean and pulse
pressure were reduced significantly, as was mean diameter. Wall shear rate was significantly elevated relative to the control state before drug infusion.

During norepinephrine injection (Fig 5), flow rate increased significantly, as did diastolic pulsatility, but pulse frequency was not affected. Mean and pulse pressures were elevated greatly, and the diameter increased in response to the pressure increase. There was a significant elevation of peak wall shear rate.

Isoproterenol infusion (Fig 6) led to a large increase in pulse rate (up to 3 Hz) and a significant increase in flow rate, accompanied by a reduction in diastolic pulsatility. There was a reduction in pressure and diameter, and again peak wall shear rate increased significantly.
Angiotensin (Fig 7) did not significantly alter pulse rate, although mean flow rate and systolic and diastolic peak flow rates increased appreciably. Pressure and diameter increased. Angiotensin did not induce significant alteration of peak wall shear rate.

**Impedance Data**

Composite impedance spectra for each drug-induced state and the associated control state before drug infusion are displayed in Fig 8. The mean modulus (peripheral resistance) and the first harmonic phase angle are two features of the impedance spectra that were markedly affected by drugs. The effects of drugs on these two quantities are displayed separately (Figs 9 and 10). An unpaired t test was used to assess the statistical significance of drug-associated alterations. The departure from control levels was significant (P<.05) for nitroprusside, norepinephrine, and isoproterenol but not for angiotensin. Nitroprusside and isoproterenol reduced the mean modulus and increased the first harmonic phase angle, whereas norepinephrine had opposite effects.

**Viscoelastic Modulus Data**

The magnitude of the viscoelastic modulus for each drug state and the control state before drug infusion are shown in Fig 11. Phase angles for the viscoelastic modulus are not displayed because the delay time for pulse travel between the dimension and pressure transducers (Fig 1) cannot be accurately estimated without knowledge of the pulse-wave velocity for each hemodynamic state. Nitroprusside and isoproterenol (vasodilators) induced a significant reduction in the magnitude of the viscoelastic modulus, whereas norepinephrine and angiotensin had the opposite effect. The values of the average modulus (in dynes per square centimeter) for the first four harmonics, between 2 and 8 Hz, for both the control and the drug state are, respectively, as follows: 1.02×10^6 and 0.34×10^6 for the control and nitroprusside, 0.99×10^6 and 0.39×10^6 for the control and isoproterenol, 0.99×10^6 and 2.40×10^6 for the control and angiotensin, and 0.88×10^6 and 3.93×10^6 for the control and norepinephrine. Consistent with these changes in arterial wall properties were associated changes in the radial pulsation of the artery (Fig 12). Radial pulsation increased significantly (P<.05) relative to control values for nitroprusside and isoproterenol and decreased slightly, but not significantly, for norepinephrine and angiotensin.

**Wall Shear Rate Data**

The changes in peak wall shear rate for each drug state relative to the control state just before drug administration are displayed in Fig 13. For comparison, the changes in peak wall shear rate predicted by Womersley's theory are also presented. The vasodilators (nitroprusside and isoproterenol) induced large increases in peak wall shear rate, which were statistically significant (P<.06) but not predicted accurately by Womersley's theory. The vasoconstrictors produced smaller, but statistically significant (P<.06), changes that were accurately predicted by Womersley's theory.

**Discussion**

Measurements of pressure, flow, diameter, and wall shear rate in the abdominal aortas of dogs have been obtained and used to characterize the hemodynamic state in response to acute administration of vasoactive drugs. Whereas pressure, flow, and diameter are hemodynamic variables that are routinely measured, wall shear rate is much more difficult to measure accurately and has rarely been measured directly in vivo. Because
WSS (viscosity x wall shear rate) is one of the two basic mechanical forces imposed on vessel walls by blood flow (pressure being the other) and it is known to play a role in flow regulation, vessel wall remodeling, and possibly arterial disease. We have measured its response to large variations in hemodynamic state. Figs 4 through 8...
indicate that it was possible to increase flow and pressure with norepinephrine, increase flow and reduce pressure with isoproterenol, maintain flow and reduce pressure with nitroprusside, increase diameter variation with nitroprusside and isoproterenol, reduce diameter variation with angiotensin, and increase pulse frequency with isoproterenol. To characterize the hemodynamic state in response to these changes, we have determined the impedance and pressure strain modulus. The nonlinear theory of oscillatory flow in straight elastic tubes16,17 (extension of Womersley's theory to elastic tubes) indicates that wall shear rate depends on the phase angle of the impedance and the vessel wall diameter variation over a cycle that is related to the pressure strain modulus. The present study provides data that allow us to test whether such relations hold in vivo in a relatively straight section of artery.

The observed changes in the impedance spectra in response to drugs (Figs 8 through 10) are not unexpected and quite in accord with the literature for both humans and animals. The mean modulus decreased 40% to 50% for the vasodilators and increased 30% to 50% for the vasoconstrictors. There was a significant positive shift in the first harmonic phase angle for the vasodilators: 20° for nitroprusside and 30° for isoproterenol. For norepinephrine, there was a relatively small decrease of 8° in the first harmonic phase angle and virtually no alteration in phase angle for angiotensin.

O'Rourke and Taylor24,25 and Cox26 made similar observations for norepinephrine and isoproterenol in dog aortas. Cox26 also considered angiotensin in dog aortas with trends similar to what we have reported. Nitroprusside and angiotensin were studied in human aortas,27,28 and again the observations were consistent with the present study.

A simple model that is consistent with the observed impedance alterations is the transmission line with a terminal resistor.15,24,29 The vasoconstrictors increase the terminal resistance; this induces greater wave reflection from the peripheral circulation and a more negative phase angle for the first harmonic of the impedance (input impedance of the model). The vasodilators reduce the terminal resistance and associated wave reflection, and this produces a positive shift in the first harmonic phase angle of the impedance. Klanchar et al.15 have simulated these effects in vitro by using a rubber tube model and a variable flow resistor, whereas Wang and Tarbell16,17 have carried out two-dimensional unsteady flow calculations for the same system. These modeling studies show that changes in impedance phase angle can induce changes in both the mean and oscillatory components of wall shear rate.

The viscoelastic modulus data for the control state (Fig 11) are consistent with limited data reported in the literature. Bergel30 and Gow and Taylor31 determined the magnitude of an elastic modulus (E1), which is related to the viscoelastic modulus (E2), which we have measured by the following relation: $E_2 = \frac{(1-\sigma^2)R_1}{2\sigma h}$, where $\sigma$ is the Poisson ratio, $R_1$ is the inside radius of the vessel, and $h$ is the vessel wall thickness. Assuming $\sigma = 1/3$ and taking a typical value of $R_1/h = 0.10$, we find $E_2 = 7.5 \times 10^5$ dyn/cm². Bergel30 and Gow and Taylor31 report the magnitude of $E_2$ in the frequency range of 1 to 3 Hz in the abdominal aorta of dogs to be $= 10^6$ dyn/cm², whereas the average of our control values for the magnitude of $E_2$ in the range of 2 to 8 Hz is $= 1 \times 10^6$ dyn/cm². Thus, our modulus data for the control state are within 25% of data reported by others.

It seems quite plausible that the vasoconstrictors would lead to an increase in the viscoelastic modulus (Fig 11, right panels), whereas the vasodilators would lead to a decrease (Fig 11, left panels). The vasoconstrictors produced an increase in pressure that would be expected to increase the viscoelastic modulus because of the passive nonlinear characteristics of the wall.32 In addition, active smooth muscle contraction in response to these drugs should contribute to increased wall stress.32 Conversely, the vasodilators reduced pressure and relaxed smooth muscle, both of which would be expected to lower the viscoelastic modulus of the wall, as observed. The relative contributions of passive and active mechanisms to alterations in the viscoelastic modulus of the wall cannot be determined from the present experiments.

Although the vasoconstrictors produced stiffer arteries, the radial displacements over a cycle were not reduced significantly (Fig 12) because the pressure pulse was elevated. On the other hand, the pressure pulse was reduced for the vasodilators, but the radial displacement increased (Fig 12) because the viscoelastic modulus was reduced sufficiently.

The present study is the first to determine the effect of vasoactive drugs on wall shear rate through direct
measurements in vivo. One concern about the wall shear rate measurement technique is that the calibration of the hot-film probe in the thoracic aorta required removing the probe from one site and reinserting it into another site with the possibility of alterations in the flush alignment of the probe, which would affect the calibration. However, the probe flange and collar (Fig 2) were designed to minimize this problem and to ensure flush alignment. The flush alignment should have been reproducible to within ±0.05 mm, the thickness of the flange at the sensor end of the hot-film probe. Although we were not able to systematically misalign the probe to determine the effect on $E_b$, Miller,3 using a similar FMHFA probe mounted on the wall of a 10-mm-

diameter model aorta in a mock circulatory loop simulating aortic flow conditions in a dog, perturbed the flush alignment by ±0.35 mm and observed a 20% perturbation in peak anemometer $E_b$ relative to its diastolic value. This suggests that errors in $E_b$ due to errors in flush alignment of our probe should be considerably less than 20%—probably less than 5%. Further proof that the flush alignment of the probe in the abdominal aorta during experiments was reproduced in the thoracic aorta during calibration can be found in the data of Figs 3 and 5. Here, we see that the wall shear rate is very close to zero during that portion of the cycle when the flow is close to zero. This provides assurance that parameter A in Equation 2 is quite accurate. One would also expect that if parameter A is accurately reproduced, then the system is flush-aligned, and that parameter B in Equation 2 should also be accurately reproduced. Indirect verification of this can be found in the data for peak wall shear rate in the control state, which is consistent with other data in the literature as discussed below.

Another concern with the wall shear rate measurements is that the flush alignment of the probe on the vessel wall might be altered by changes in arterial pressure associated with vasoactive drugs. We don’t believe that this was a significant problem because, for example, the nitroprusside data (Fig 4) show that the ratio of the peak retrograde flow rate during diastole to the peak flow rate during systole (≈3/10 in Fig 4) is nearly the same as the ratio of the peak shear rate
during retrograde flow (which appears positive because the hot-film probe does not distinguish direction) to the peak shear rate during systole. If the probe alignment had been altered significantly in the low-pressure drug state, there would have been an offset in the measured wall shear rate that would have altered this ratio. A similar argument can be made for other drug states (see Figs 3 and 5 through 7).

There were two previous studies in which wall shear rate was measured by FMHFA in the thoracic aorta of dogs3,14 under anesthesia but without vasoactive drugs. Ling et al13 reported peak wall shear rates between 2000 and 4000 s⁻¹, whereas Miller and Hollis14 obtained similar results for peak wall shear rate ranging between 2628 and 4492 s⁻¹. These values are not inconsistent with peak wall shear rates in the range of 636 to 3579 s⁻¹ (mean, 1835 s⁻¹) measured in the control state in the abdominal aorta of dogs in the present study. In fact, on the basis of Womersley’s theory of oscillatory flow in straight rigid tubes,22 it is expected that peak wall shear rate should be higher in the thoracic aorta than in the abdominal aorta because of higher unsteadiness. Unsteadiness is characterized by Womersley’s unsteadiness parameter, α=a√ω/ν. When α is large, as it is in the aorta, it can be shown34 by Womersley’s theory that peak wall shear rate is directly proportional to α or, equivalently, to the vessel radius a. Since the radius of the thoracic aorta is typically 40% greater than the radius of the abdominal aorta, it is not surprising that higher values of peak wall shear rate are observed in the thoracic aorta.

The peak wall shear rate measured in the abdominal aorta under control conditions in the present study was 1835±153 s⁻¹, whereas the peak wall shear rate calculated from Womersley’s theory under control conditions using measured flow and diameter data was 2741±152 s⁻¹ (Fig 13). Thus, the measured peak wall shear rate was 33% lower than the value computed by Womersley’s theory. Tarbell et al35 compared the predictions of Womersley’s theory for peak wall shear rate with the measurements of Miller and Hollis14 in the thoracic aorta of dogs and found that the measured values were ≈15% lower than the values computed by Womersley’s theory. It seems that Womersley’s theory provides a reasonable estimate of peak wall shear rates in both the thoracic and abdominal aorta of dogs under control conditions in which the radial wall motion is relatively small (Fig 12). The larger deviations between measurements and theory for the abdominal aorta reported in the present work may be due to the influence of flow through the renal arteries, which are proximal to the abdominal aortic measurement site. As pointed out by Pedersen et al,36 who conducted in vitro studies of human abdominal aortic flow, the renal arteries may induce vortexes and flow separation in the suprarenal aorta that would not be accounted for in Womersley’s theory. On the other hand, they observed that flow in the infrarenal aorta was less complicated with predominantly straight streamlines, which would be consistent with Womersley’s theory.

All of the vasoactive drugs induced statistically significant changes in peak wall shear rate (Fig 13). The vasodilators led to large increases, whereas the vasoconstrictors produced either a small increase (norepinephrine) or a small decrease (angiotensin II) in peak wall shear rate. It is interesting to note that the drug-induced changes were predicted accurately by Womersley’s theory for the vasoconstrictors (norepinephrine and angiotensin) but not for the vasodilators (nitroprusside and isoproterenol).

The vasoconstrictors actually produced less vessel wall motion than did the absence of drugs (Fig 13), which would suggest that Womersley’s rigid tube theory would be more appropriate to describe flow in the presence of these drugs. In addition, angiotensin and norepinephrine produced increases in flow rate. Pedersen et al36 observed that infrarenal flow became more streamlined, with only slight flow reversal as flow rate was increased under exercise conditions, suggesting that flow disturbance in the abdominal aorta induced by the renal branches was diminished at higher flow rates. Thus, higher flow rates associated with angiotensin and norepinephrine might be expected to produce streamline flow patterns consistent with Womersley’s theory.

The vasodilators led to reductions in pressure from 110/60 mm Hg to 65/35 mm Hg for nitroprusside and 80/40 mm Hg for isoproterenol. At these lower pressures, we did not observe vessel collapse or any obvious distortion of vessel cross section from circular, which might have affected velocity profiles and wall shear.

Fig 13. Bar graph showing the percent change in peak wall shear rate for drugs relative to control data ([drug−control]/control). The open bars are based on flush-mounted hot-film anemometry measurements, and the shaded bars are based on experimental measurements of flow rate and vessel diameter and a blood viscosity of 0.039 poise using Womersley’s theory.18 The control values of the peak wall shear rate are 1835±153 s⁻¹ for the experimental measurement and 2741±152 s⁻¹ for Womersley’s theory.
rates. This is consistent with other reports\textsuperscript{20}(p442),\textsuperscript{2}(p169) that show maintenance of circular cross section in the abdominal aorta of dogs down to 15 mm Hg.

The deviations between Womersley’s theory and the vasodilator measurements might be accounted for by effects induced by vessel wall motion and changes in impedance phase angle. Recall that radial wall motion increased significantly relative to the control value for the vasodilators and actually decreased slightly for the vasoconstrictors (Fig 13). In addition, the vasodilators produced large positive increases in the phase angle (Fig 10). However, the nonlinear theory of oscillatory flow in elastic straight tubes\textsuperscript{28} actually predicts an ~20% reduction in the wall shear rate amplitude relative to the Womersley theory prediction for the vasodilator flow conditions. Thus, it appears that increased wall motion and impedance phase angles in straight vessels cannot explain the deviation of wall shear measurements from Womersley’s theory for vasodilators.

However, it may be that increased vessel wall motion at the renal branches produces greater flow disturbances in the abdominal aorta, as has been observed by Reneman et al\textsuperscript{37} at the transition from the common to the internal carotid artery. The drugs may also alter flow partitioning to the renals, which in turn could affect abdominal aortic flow patterns. At the present time, these remain hypotheses to explain the significant deviations between predictions of Womersley’s theory and measured wall shear rates in the abdominal aorta when vasodilators have been infused.

It is well known that vasoactive drugs affect blood pressure and flow in arteries. The present study has shown that wall shear rate (stress) can also be affected by vasoactive drugs. Although the mechanism is not completely understood, nitroprusside and isoproterenol induce significant increases in peak wall shear rate (stress) in the abdominal aorta of dogs. The mechanical effect of vasodilators on arteries is normally thought to be a reduction in pressure\textsuperscript{5}; however, the present study suggests that elevation of WSS may be a significant concomitant factor in the abdominal aorta.

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**Appendix**

A procedure for determining the constant C in the dynamic model of the FMHFA (Equation 4) is presented in this appendix. It is assumed that constants A and B have been determined in steady-state experiments.

For a hot-film anemometer, the measured quantity is the electrical power required to maintain a constant film temperature. This power is given by $E_v^2/R$, where $E_v$ is the voltage drop across the film and R is the resistance of the film. The electrical power is transformed into heat, which is convected away by the fluid and also lost to the substrate of the film by conduction. Since the film resistance is maintained constant when the anemometer bridge is “on,” we can write

\begin{equation}
E_v^2 = N_h + N_l
\end{equation}

where $N_h$ represents the heat convected away by the fluid (times the probe resistance) and $N_l$ denotes the heat loss to the substrate (times the probe resistance). $N_l$ is identical to parameter A in Equations 2 and 4 in the text.

When the hot-film probe is turned on, two dynamic processes must be considered: the dynamics of the thermal boundary layer ($N_h$) and the dynamics of the heat loss to the substrate ($N_l$). The transient behavior of the thermal boundary layer is related to the wall shear rate by Equation 4 in the text. On the other hand, the dynamics of the substrate loss should be independent of the wall shear rate. On the basis of this idea, we can isolate the dynamics of the thermal boundary layer by running the turn-on experiments under two different steady wall shear rates, $S_1$ and $S_2$. The corresponding experimental $E_v$ values are recorded as $E_v(t)$ and $E_v(t)$. Since the dynamics of the heat loss to the substrate are independent of wall shear rate, the dynamics of $E_v(t)-E_v(t)$ should only be related to the transient behavior of the thermal boundary layer. The theoretical prediction of $E_v(t)-E_v(t)$ can be obtained by solving the following equations\textsuperscript{21}:

\begin{equation}
\frac{d\psi_1}{dt} = \frac{2}{B} \left( 1 - S_1 \psi_1^{3/2} \right)
\end{equation}

\begin{equation}
\frac{d\psi_2}{dt} = \frac{2}{B} \left( 1 - S_2 \psi_2^{3/2} \right)
\end{equation}

subject to the initial conditions

\begin{equation}
\psi_1(t=0) = 0; \, \psi_2(t=0) = 0
\end{equation}

and noting that

\begin{equation}
E_v(t)-E_v(t) = B \left( \frac{1}{\sqrt{\psi_1}} - \frac{1}{\sqrt{\psi_2}} \right)
\end{equation}

In the above equations,

\begin{equation}
B/\sqrt{\psi_1} = N_h, \, B/\sqrt{\psi_2} = N_l
\end{equation}

where $N_h$ and $N_l$ are the convective heat losses for shear rates $S_1$ and $S_2$, respectively.

The parameter C can be determined by minimizing the square of the deviations between the theoretical prediction (described above) and the experimental measurement of $E_v(t)-E_v(t)$. A typical result is presented in Fig 14.
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