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Gender Differences in Wall Shear–Mediated Brachial Artery Vasoconstriction and Vasodilation

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OBJECTIVES We sought to investigate wall shear rate (WSR) and brachial artery diameter (BAD) changes simultaneously and to determine whether any gender differences exist in arterial reactivity.

BACKGROUND Wall shear rate/stress and arterial reactivity are rarely assessed at the same time. Furthermore, flow-mediated vasoconstriction has received less attention than flow-mediated vasodilation in humans.

METHODS A new noninvasive evaluation of WSR in the brachial artery, using multigated, pulsed Doppler velocimeter and a double-transducer probe moved and fixed by a robotic system, was developed.

RESULTS The validity of the system was tested in vitro with calibrated tubes and showed a high correlation ($r = 0.98$, $p < 0.001$). In 10 men and 10 women of similar age, induction of low and high shear rates by forearm occlusion produced significant vasoconstriction and vasodilation, respectively. The time lag for maximal BAD changes was 3 min for vasoconstriction and 1 min for vasodilation. A greater half-time for vasodilation (96 ± 6 for men and 86 ± 12 s for women) than for shear rate (31 ± 5 s for men and 34 ± 4 s for women) was observed after discontinuation of occlusion. Relative BAD was correlated with WSR changes, showing a significantly higher slope in women than in men ($p < 0.01$). Moreover, a larger normalized arterial diameter per shear rate was observed for vasoconstriction ($p < 0.01$) and vasodilation ($p < 0.01$) in women than in men.

CONCLUSIONS Shear-mediated arterial vasodilation and vasoconstriction were more pronounced in women than in men, suggesting different gender-related sensitivity in the regulation of large-artery vascular tone. (J Am Coll Cardiol 2001;38:1668–74) © 2001 by the American College of Cardiology

Postischemic dilation of the brachial artery was reported to be greater in premenopausal women than in men (1,2). In addition, flow-mediated vasodilation was found to be decreased in postmenopausal women and improved after estrogen supplementation (3,4). These studies were restricted to arterial changes induced by an increase in blood flow during reactive hyperemia. However, there is evidence that acute induction of low flow constricts the brachial artery (5,6). As yet, there are no studies that examine the possible gender difference in flow-induced arterial constriction during forearm occlusion.

Another important issue of flow-mediated arterial changes is that the stimuli inducing reactive constriction or dilation (i.e., shear rate/stress) are rarely measured at the same time as arterial responses. In addition, flow is not independent of diameter, because it is calculated from diameter and velocity measurements.

The development of multigated ultrasonography has made possible the transcutaneous assessment of the velocity profile (i.e., the distribution of instantaneous velocity along the vessel's cross section), as well as assessment of the shear rate at discrete intervals during the cardiac cycle (7). In the present report, we used a multigated, pulsed Doppler velocimeter, which offers unique features to measure, in real time, a complete velocity profile and to assess wall shear rate (WSR) and brachial artery diameter (BAD) simultaneously. In addition, a robotic system was applied to select, translate and keep in place, over the course of the artery, the ultrasonic probe, thus improving the precision of the measurements.

The goals of this study were: 1) to test whether shear-induced constriction and dilation exist in the brachial artery of women and men; and 2) to determine the time course of arterial changes of low and high wall shear during and after occlusion of the forearm circulation.

In this study, we hypothesized that acute low and high shear stress would be associated with gender differences in arterial constriction and dilation.

METHODS

Ultrasonic multigated velocimetry. The multigated Doppler velocimeter (DOP1000, Signal Processing, Lausanne, Switzerland) is able to instantaneously measure velocity profiles of a peripheral large artery based on the following characteristics: emission frequency of 10 MHz; 248 select-

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Abbreviations and Acronyms

BAD = brachial artery diameter
BMI = body mass index
DBP = diastolic blood pressure
HR = heart rate
SBP = systolic blood pressure
WSR = wall shear rate

able pulse repetition frequency; a number of gates between 10 and 224; and minimal spatial and temporal resolutions of 0.3 mm and 3 ms, respectively. The number of emissions per profile can be selected at any value between 8 and 512, and this system can be controlled by an external trigger or electrocardiographic synchronization. A previously developed double-transducer probe formed between them an angle of 120° permits adjustment of the incident angle of the ultrasonic beam at 60 ± 1° to the arterial axis (8,9).

The velocimeter records data profiles in ASCII format. Off-line signal processing was carried out using an algorithm enabling the calculation of the arterial diameter and shear rate, developed in MatLab 5.3 (Math Works Inc., Natick, Massachusetts). From the acquired instantaneous velocity profiles, a mean profile was obtained. Mean BAD was calculated from the intersection of the zero velocity line and the straight lines obtained from linear extrapolation of the first portion of the velocity profile at the anterior and posterior walls. Mean WSR was estimated from averaged peak values of the derivatives of the velocity profile at the anterior and posterior walls.

Robotic system. The robot, a prototype called Hippocrate (SINTERS, Toulouse, France) (10), was compliant with European Community marking, intrinsically safe and approved for clinical investigation by the Ethics Committee of Henry Mondor Hospital. Practically, Hippocrate consists of a robotic arm with 6 degrees of freedom adjustment—three in translation and three in rotation by minimal steps of 0.1 mm and 0.5°, respectively. The transducer probe was attached to the robotic arm for its precise micromanipulation and positioning. The system allows movement of the probe in a step-by-step manner on the arterial target, while applying a programmable and constant force, as well as documentation of its successive spatial location. Force control is necessary to provide good and reproducible conduction of the ultrasonic signals, while preventing arterial deformation. A joystick device permits the selection, translation and rotation of the ultrasonic probe on the six axis positions.

Procedure. First of all, the arm containing the ultrasonic probe was moved from the home position to the vicinity of the measuring zone—the brachial artery over the antecubital fossa. The desired force (60 to 100 *g*), the step-to-step displacement and the degree of rotation were designed on the computer. When the configuration of the procedure was stored, the robotic arm was translated perpendicularly to the plane formed by the two emitted ultrasonic beams until the apparition of a velocity profile on one transducer. Thereafter, the probe was translated in the same direction to obtain a velocity profile from the second transducer. With the rotation system, the probe was adjusted until the ultrasonic plane was parallel to the vessel's axis. Then, the probe was translated by intervals of 0.1 or 0.2 mm from the proximal to the distal wall to place the probe at half of the vessel's diameter. In this position, the probe was rotated around an axis perpendicular to its plane until the responses on each transducer were equal in absolute values. In this case, the ultrasonic incidence angle was 60°.

Laboratory testing. To validate the measurements obtained with the multigated velocimeter, in vitro experiments were performed on a hydrodynamic model. For this, laminar flow (14 to 60 ml/min) of viscous fluid suspension of silicon oil particles in water (2.19 mPa · s) was imposed inside rigid, calibrated, rectilinear ducts (4, 5, 6, 7 and 8 mm) and immersed in a water tank.

Subjects and study design. Twenty healthy volunteers (10 women [22 to 50 years old] and 10 men [23 to 45 years old]) from the hospital staff were enrolled in this study. Informed consent for the study was obtained from the subjects after they were given a detailed description of the procedure. The 10 women had regular menstrual cycles for more than three months before this study. All were in the first phase of their menstrual cycle, but no blood samples were obtained to confirm this state. All subjects were asymptomatic, normotensive and nondiabetic and were not taking any medications (except for 5 women using oral contraceptives). All subjects abstained from alcohol and caffeine for 8 h before the study. The investigation was performed with the subject in the supine position, at a controlled room temperature of 22 ± 1°C, after 15 min of rest, with the right arm fixed to restrict movement at the mid-thoracic level. After baseline measurements were obtained after 15 min, an occluding cuff placed ~8 cm distal to the site of brachial artery determination was inflated to a pressure of 250 mm Hg for 300 s. The velocity profile was determined for each probe at an interval of 60 s for 300 s during arrest of forearm circulation and at 20, 60, 90, 120, 180, 240, 300, 360, 480 and 600 s after release of arterial occlusion. Figure 1 shows an example of instantaneous velocity profiles before, during and after occlusion. Blood pressure was monitored in the left arm at the same time as the instantaneous velocity profile acquisition by use of an automated blood pressure recorder (Omron HEM 705CP, Tokyo, Japan).

Statistical analysis. Data are expressed as the mean value ± SEM. Group differences were determined by the Student *t* test. Linear regression analysis was performed using the least squares method. The differences in slopes were determined by analysis of covariance. Agreement between the actual diameter of the calibrated tubes and the calculated multigated velocimetric measurement was analyzed according to the Bland-Altman approach (11). The time course differences were determined by repeated measures analysis of variance, followed by the Bonferroni post hoc test. The half-time decay (in seconds) of WSR and BAD during hyperemia was analyzed

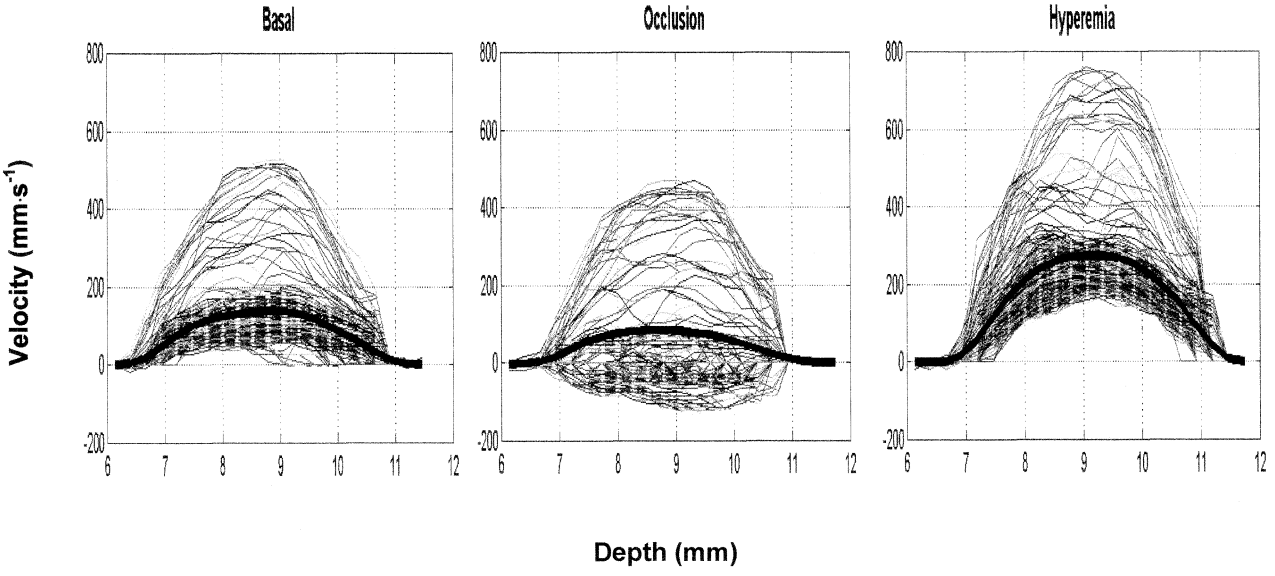

Figure 1. Representative tracings of brachial artery velocity profiles for one subject assessed by Doppler multigated velocimetry at baseline **(left)**, during forearm occlusion at 180 s **(center)** and after 20 s of reactive hyperemia **(right)**. **Bold lines** represent the mean value of at least 200 velocity profiles at each condition.

with a semi–log-plot. Multivariate regression analysis with WSR-induced dilation or constriction as the dependent variable and age, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) as the independent variables were evaluated. Statistical significance was set at $p < 0.05$.

RESULTS

Laboratory and clinical testing. A strong positive linear relationship was found between the actual diameter of the calibrated tubes and those calculated from the velocity profile algorithm ($r = 0.98$), with a slope of 0.99 ± 0.01 and an intercept of 0.24 ± 0.11 mm. The mean difference (ducts minus multigated velocimeter) was -0.21, with a 95% confidence interval of -0.69 to 0.27 mm (Fig. 2).

The intrasubject and intersubject variabilities for 200, 400 and 1,000 velocity profiles obtained at each probe in 16 subjects are depicted in Table 1. The mean average was <3% for BAD and <6% for WSR. To evaluate the reproducibility, the examination was repeated two times for each transducer at a one-week interval in nine subjects. The coefficients of variation for repeated measurements for BAD and WSR were <4% and 7% at baseline, 3% and 7% at 300-s occlusion and 2% and 6% at 20-s hyperemia, respectively (Table 1).

Clinical study. No differences in age, BMI, DBP, HR, WSR or blood flow were observed in women as compared with men. Systolic blood pressure ($p < 0.05$) and mean BAD ($p < 0.01$) were higher in men than in women (Table 2).

Shear-mediated constriction. Sixty seconds after arterial occlusion, WSR and blood flow decreased from 91 ± 12 to

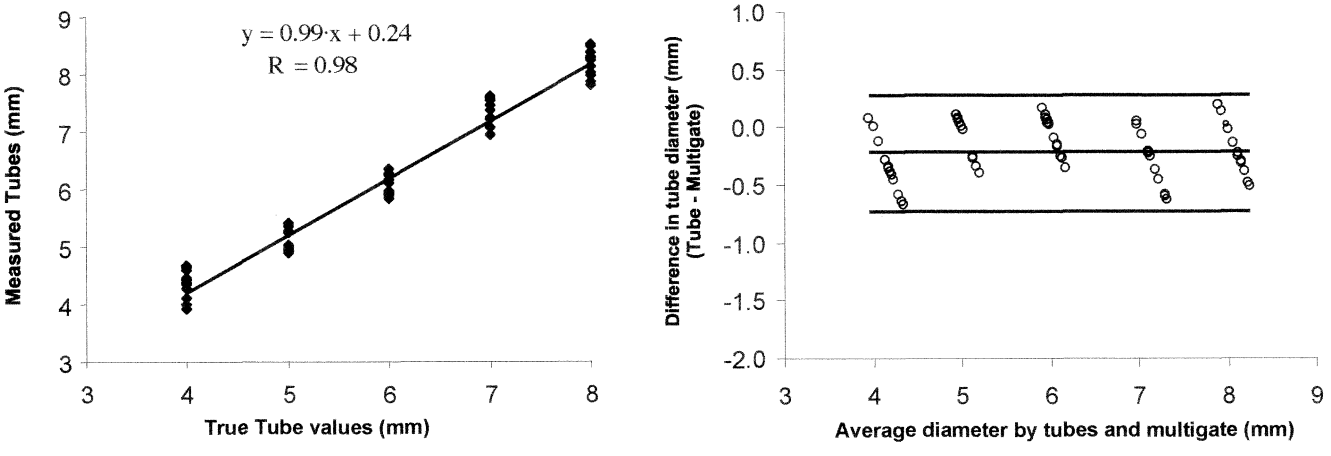

Figure 2. (Left) Measured diameter obtained by Doppler multigated velocimetry, as compared with true tube values. **(Right)** Difference in mean value between the measured diameter obtained by Doppler multigated velocimetry and the actual tube diameter value.

Table 1. Intrasubject and Intersubject Variabilities and Reproducibilities

	Variability*			Reproductibitity*		
	200 Profiles (n = 16)	400 Profiles (n = 13)	1,000 Profiles (n = 12)	Basal Condition (n = 9)	Occlusion, 300 s (n = 9)	Hyperemia, 20 s (n = 9)
Brachial diameter	1.4 ± 0.25	2.1 ± 0.42	2.8 ± 0.58	3.7 ± 0.3	2.9 ± 0.47	1.7 ± 0.1
Brachial shear rate	4.8 ± 0.55	5.8 ± 0.44	5.8 ± 0.38	6.1 ± 0.6	6.4 ± 0.73	5.8 ± 0.37

*Coefficient of variation (%). Data are presented as the mean value ± SEM.

42 ± 7 s^{-1} and from 42 ± 8 to 11 ± 1 ml/min ($p < 0.001$) in women and from 89 ± 18 to 28 ± 5 s^{-1} and from 51 ± 10 to 10 ± 2 ml/min ($p < 0.001$) in men, respectively. Although the decrease in WSR was lower in women than in men ($p < 0.01$), blood flow did not differ. The reduction in WSR and blood flow persisted during the 300 s of cuff occlusion and was associated with a significant reduction in the mean arterial diameter (Fig. 3). The maximal diameter reduction was observed at 180 s—from 4.18 ± 0.15 to 3.43 ± 0.17 mm in women ($p < 0.001$) and from 4.62 ± 0.11 to 3.86 ± 0.12 mm ($p < 0.001$) in men. The absolute change in diameter was not different between women and men. However, because the decrease in WSR was lower in women than in men, the percent change in BAD induced by the decrease in WSR was normalized for each subject in both groups (percent change in BAD/percent change in WSR × 100). The ratio of BAD to WSR was significantly greater in women than in men (39 ± 2.8 for women and 19 ± 1.2 for men; $p < 0.01$) (Fig. 4). Systolic blood pressure, DBP and HR did not change significantly during occlusion in women (108 ± 3 and 68 ± 2 mm Hg and 72 ± 3 beats/min, respectively) and men (119 ± 2 and 70 ± 3 mm Hg and 67 ± 3 beats/min, respectively).

Shear-mediated dilation. Twenty seconds after release of occlusion, WSR and blood flow increased to 211 ± 28 s^{-1} and to 132 ± 24 ml/min ($p < 0.001$ vs. baseline) in women and to 259 ± 33 s^{-1} and 163 ± 19 ml/min ($p < 0.001$ vs. baseline) in men, respectively. In response to the increase in WSR, maximal arterial dilation was noted at 60 s and reached 4.64 ± 0.19 mm in women ($p < 0.001$ vs. baseline) and 4.94 ± 0.12 mm in men ($p < 0.001$ vs. baseline). The absolute (0.45 ± 0.13 and 0.32 ± 0.11 mm; $p < 0.05$) and percent change (11 ± 4% and 7 ± 3%; $p < 0.01$) in BAD was significantly increased in women as compared with men. The ratio of BAD to WSR changes was significantly greater in women than in men (9.5 ± 1.2 for women and 4.5 ± 0.8 for men; $p < 0.01$) (Fig. 4). The return of BAD to the basal condition (86 ± 12 for women and 96 ± 19 s for men) was slower than that of WSR (34 ± 4 for women and 31 ± 5 s for men; $p < 0.05$) (Fig. 3). Systolic blood pressure, DBP and HR did not change significantly during release of occlusion in women (110 ± 2 and 67 ± 2 mm Hg and 72 ± 3 beats/min, respectively) and men (113 ± 1 and 64 ± 2 mm Hg and 69 ± 3 beats/min, respectively).

Multivariate and regression analyses. On multivariate analysis of the group as a whole or in separate gender groups, shear-induced constriction or dilation was not significantly related to age, BMI, HR, SBP or DBP.

The percent changes in BAD were positively correlated with the percent changes in shear rate in women ($y = 0.1842 \times +0.3064$; $r = 0.81$, $p < 0.01$) and men ($y = 0.0734 \times -3.964$; $r = 0.79$, $p < 0.01$), with a regression line significantly different between groups ($p < 0.01$) (Fig. 5).

Table 2. Characteristics of Study Groups

	Women	Men
Age (years)	32 ± 3	34 ± 2
BMI (kg/m^2)	21.5 ± 0.8	22.5 ± 0.8
SBP (mm Hg)	106 ± 3	115 ± 2*
DBP (mm Hg)	64 ± 2	68 ± 2
HR (beats/min)	71 ± 2	70 ± 4
Brachial artery diameter (mm)	4.18 ± 0.15	4.62 ± 0.11†
Brachial wall shear rate (s^{-1})	91 ± 12	89 ± 18
Brachial blood flow (ml/min)	42 ± 8	51 ± 10

*$p < 0.05$ and †$p < 0.01$, compared with women. Data are presented as the mean value ± SEM.

BMI = body mass index; DBP = diastolic blood pressure; HR = heart rate; SBP = systolic blood pressure.

DISCUSSION

The main finding of this study is that women had more pronounced shear-mediated arterial vasodilation and vasoconstriction, as compared with men. A distinctive feature of our work is that the arterial diameter variations are expressed as a result of changes in WSR, because shear forces are the real effectors on the endothelial surface. The gender difference in shear-dependent modulation of BAD during ischemia and hyperemia was supported by the greater diameter per WSR changes for either vasoconstriction or vasodilation, as well as the higher slope, in women as compared with men, of a strong linear correlation between relative changes in WSR and BAD. A greater flow-mediated vasodilation has been previously documented in women as compared with men. During the normal menstrual cycle, flow-mediated vasodilation increases significantly during the follicular and luteal phases, when serum estradiol levels are high (1). In addition, reduced flow-mediated dilation with aging was reported to appear earlier in men as compared with women (2). The greater shear-mediated vasoconstriction in women, as compared with men, is an original finding of the present investigation. The effect of low flow on the arterial diameter has received less attention in clinical investigation. Previous studies have clearly demonstrated that high flow dilates and low flow constricts the brachial artery (5,6). Enhanced constriction of

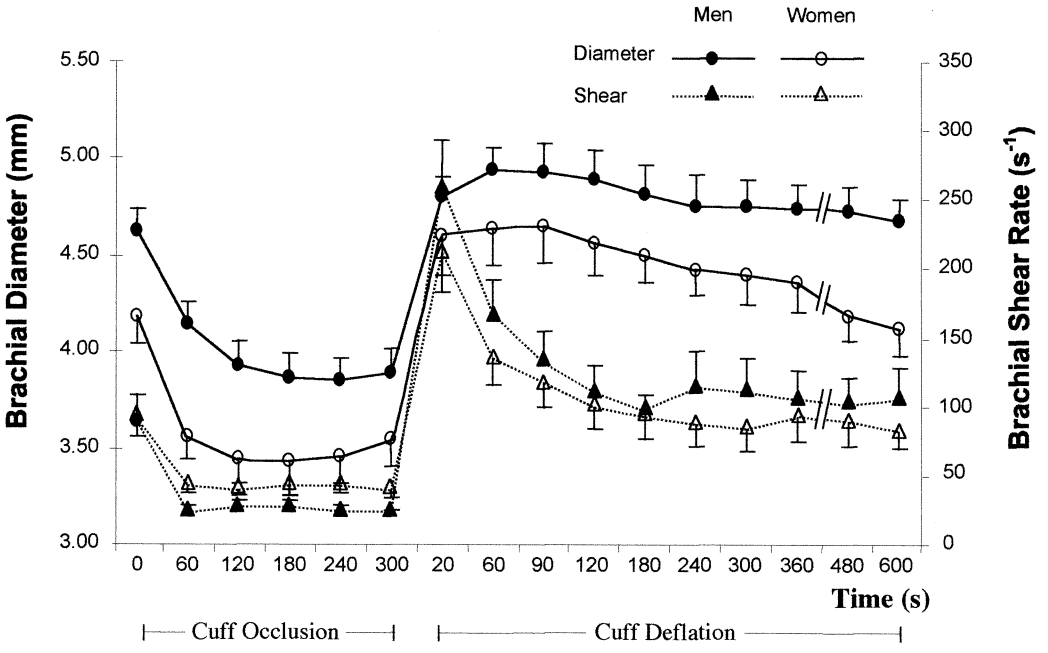

Figure 3. Time course of the entire duration of brachial wall shear rate and diameter measurements at baseline and during occlusion and reactive hyperemia in men and women.

the brachial artery in response to acute induction of a low-flow state was described in hypercholesterolemic subjects (12), an effect that was attenuated with hepatic hydroxymethyl glutaryl coenzyme A reductase inhibitors (13).

There are several lines of evidence that endothelial vasodilator functions are modulated by estrogen. Estrogen administration improves endothelium-dependent relaxation by increasing production/release, or less degradation, of nitric oxide (3,14). Other potential mechanisms of estrogen on vasodilation include higher stimulation of endothelial potassium channels (15), reduction of superoxide anion production (16) or upregulation of superoxide dismutase (17). The mechanisms of increased shear-mediated vasoconstriction in women cannot be addressed by the present study design. Endothelium-dependent contractions were explained either by withdrawal of the effect of endothelium-derived relaxation factors or by production of endothelium-contracting factors (e.g., superoxide anions, thromboxane A_2 and endothelin-1) (18).

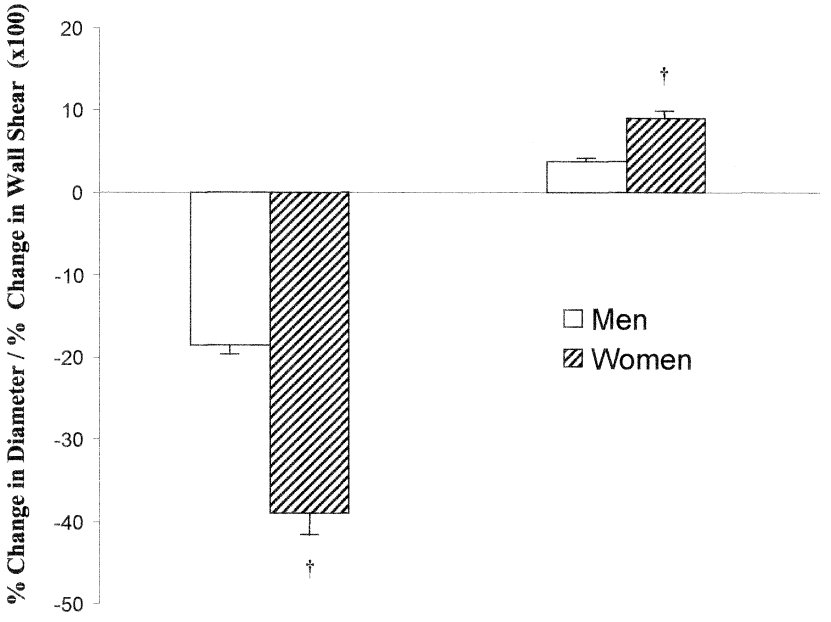

Figure 4. (Left bars) Changes in brachial diameter during arterial occlusion at 3 min, normalized for changes in wall shear rate at the same time. **(Right bars)** Changes in diameter after 1-min release of arterial occlusion, normalized for the maximal changes in wall shear at 20 s. †$p < 0.01$.

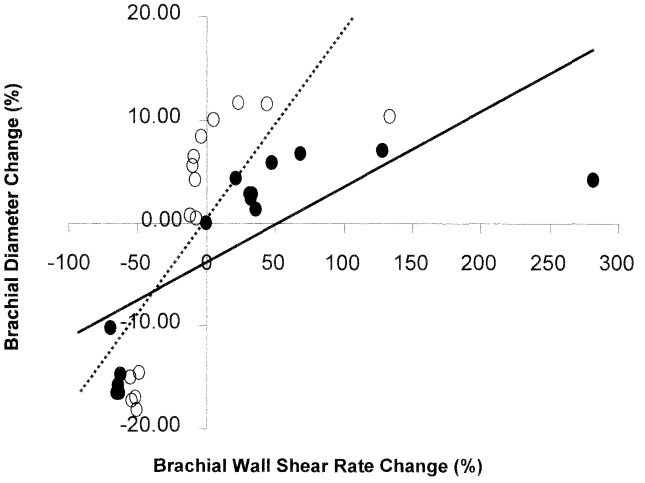

Figure 5. Scatterplot showing regression lines between brachial artery diameter and shear rate changes during the entire time course of the study (see Fig. 3). Each point for women and men corresponds to the mean percent change from baseline of the 5 measurements obtained during occlusion and the 10 measurements obtained after release of the occlusion. **Solid circles** represent men: $y = 0.0734 \times -3.964$, $r = 0.79$, $p < 0.01$; **open circles** represent women: $y = 0.1842 \times +0.3064$, $r = 0.81$, $p < 0.01$. Slope difference: $p < 0.01$. Note that the maximal increase in shear in men (282 ± 62%) and women (131 ± 28%) at 20 s is reached before the maximal increase in diameter. The exclusion of these points did not affect the significance of the regression.

Time course for shear-mediated arterial constriction and dilation. Although WSR declines and rises rapidly during occlusion and release of the forearm circulation, time lags for BAD changes were observed. Shear-induced maximal vasoconstriction occurred 3 min after occlusion, whereas maximal shear-induced vasodilation appeared 1 min after release of the forearm occlusion. The latter was in line with the time delay reported for peak vasodilation in experimental and human studies (6,19), as well as the biologic half-time for flow-mediated release of endothelial relaxing factors (20). The delayed vasoconstrictor response of the brachial artery observed in the present study needs further investigation to determine whether the acute regulation of the arterial diameter requires a longer time scale for contracting factor release. Previous studies have shown that a rapid response to increased shear-related vasorelaxation was observed with nitric oxide and prostacyclin, whereas the potent vasoconstrictor endothelin-1 appears to be reduced by an increase in shear stress and released by low shear stress on a much longer time course (21).

When peak WSR declines, BAD does not immediately return completely to the predilation size. The half-time of vasodilation after discontinuation of forearm occlusion was larger than the half-time of wall shear. This result reinforces the hypothesis that the endothelium sensed wall shear stress, thus releasing vasodilating substances to restore its values to those experienced before the change in flow. The acute vasodilation of the arterial lumen by shear stress probably limits the pressure increase induced by the rise in blood flow, thus restraining mechanical energy losses. There is a possibility that changes in wall shear stress may induce a myogenic response due to transmural pressure modification. However, in our study, shear-mediated vasoconstriction or vasodilation occurred independently of changes in blood pressure.

Clinical significance. Although flow-induced vasodilation is frequently used to characterize endothelial function, decreased flow and low shear stress are most often associated with endothelium-dependent vasoconstriction (22), intimal hyperplasia (23) and accelerated atherosclerosis (24,25). Patients with unstable angina and myocardial infarction usually have an abrupt reduction in coronary flow (26). The vasoconstriction and possible consecutive release of contracting factors induced by low shear stress may further impede coronary flow and aggravate heart disease.

The epidemiologic observation that cardiovascular disease is more frequent in men and postmenopausal women than in premenopausal women suggests vascular protective effects of women's sex hormones (27). However, it was also reported that women who develop coronary artery disease have a poorer prognosis as compared with men, with more early deaths after acute myocardial infarction and higher in-hospital mortality rates after coronary angioplasty, atherectomy or bypass surgery (28). It was also observed that after chest pain, women are more likely than men to have normal coronary artery angiograms (29). In addition, myocardial ischemia was common during intracoronary ultrasonography in women with and without coronary artery disease (30). From the results of this study, we cannot conclude how significant is the hyper-responsiveness of the brachial artery to render women more vulnerable than men to the development of higher coronary vasoconstriction in the presence of coronary artery disease. Further studies are required to determine whether shear-dependent vasoconstriction could be related to these observations.

Study limitations. A first possible limitation of the current study is related to the determination of BAD and WSR with the DOP1000. To remove the low frequency components generated by the movements of the vessel walls without losing the low blood flow velocities close to the wall (7), a digital second-order high-pass filter is used. This filter is set up to achieve a cut-off frequency near PRF/64, where PRF is the pulse repetition frequency of the ultrasonic emissions. This solution allows a sufficient dynamic range enabling measurement of low velocities near the walls. Because of the limited resolution due to the finite size of the sample volume (7), the mean WSR was estimated from the average peak values of the derivative of the velocity profile at the anterior and posterior walls. The association between the double-transducer probe and the robotic system serves to improve the reliability of these measurements. This was demonstrated by the low variations of WSR—namely, the arterial diameter—when 200, 400 or 1,000 velocity profiles were determined. In addition, the mean difference in diameter obtained with the calibrated tubes was <3.5%, which is much smaller than the mean difference between the baseline value and vasoconstriction and the baseline value and

vasodilation, as well as the difference between men and women.

Our approach is limited by the fact that blood viscosity was not measured. Because shear stress is dependent on both shear rate and fluid viscosity, an increase or decrease in either should cause parallel changes in arterial reactivity. The expected lower blood viscosity in women (31) may still induce lower shear stress, without changing the main results observed in the study. A final limitation of our study was the lack of provocative endothelium-independent vasodilation and constriction, because gender differences of the sensitivity of the vascular smooth muscle are another possible mechanism of shear-induced release of vasoactive substances.

Conclusions. This study provides an original method to assess WSR and arterial reactivity simultaneously in humans. Shear-mediated arterial vasodilation and vasoconstriction were more pronounced in women than in men, which suggests different gender sensitivities in the regulation of large-artery vascular tone. Further investigation in a larger sample of subjects is required to confirm the observation of higher shear-dependent vasoconstriction of the brachial artery in women and to determine the mechanism of these gender differences.

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