Flow-Mediated and Reflex Changes in Large Peripheral Artery Tone in Humans

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Studies of peripheral blood vessels in humans have focused primarily on regulation of blood flow and vascular resistance, which are thought to reflect small vessel caliber. Recent studies in animals have identified flow-mediated and neurogenic changes in large artery diameter. This study tested for flow-mediated dilatation and reflex constriction of the brachial artery in humans. A dual-crystal pulsed Doppler system was used to measure brachial artery diameter and blood flow proximal to the antecubital fossa. To test for flow-mediated dilatation, flow through the brachial artery was altered by an occluding cuff placed on the forearm distal to the site of brachial artery flow and diameter measurement. Control blood flow was 123±20 ml/min, and brachial artery diameter was 4.74±0.17 mm (mean±SEM). By inflating the distal occluding cuff (distal circulatory arrest), flow was reduced through the brachial artery to 21±5 ml/min (p<0.005), and brachial artery diameter was reduced to 4.35±0.20 mm (p<0.001). By deflating the distal occluding cuff after 10 minutes (reactive hyperemia), brachial artery flow was increased to 358±55 ml/min (p<0.001), and diameter was increased to 5.6±0.19 mm (p<0.001). These interventions did not change systemic arterial pressure and, as measured in three subjects, caused only small changes in local brachial artery distending pressure. Thus, both increased and decreased brachial artery blood flow produced significant changes in brachial artery diameter without altering arterial distending pressure. These data provide evidence for flow-mediated dilatation in humans. Reflex constriction was assessed by responses to lower-body negative pressure (−20 mm Hg) and the cold pressor test. Both reflex stimuli significantly (p<0.001) reduced flow and brachial artery diameter. To determine whether or not these reflex stimuli caused constriction independent of reduced flow, lower-body negative pressure and the cold pressor test were performed during distal circulatory arrest (i.e., when brachial artery flow could not change). The cold pressor test, but not lower-body negative pressure, caused constriction beyond that attained by distal circulatory arrest alone (p<0.005). Thus, brachial artery constriction with the cold pressor test may involve direct sympathetic constriction, but brachial artery constriction during lower-body negative pressure can be explained by reduced flow alone. In summary, this study demonstrates that a tonically active, flow-mediated dilatation occurs independent of changes in distending pressure in a large peripheral artery in humans. Further, reflex stimuli cause constriction of the brachial artery that may involve direct sympathetic constriction or may be secondary to reduced flow. (Circulation 1989;79:93–100)

Studies of peripheral blood vessels in humans have focused primarily on regulation of blood flow and vascular resistance, which are thought to reflect primarily small vessel tone. However, there is evidence that the tone of large arteries, as well as arterioles, may be regulated actively. Studies in humans and animals and isolated vessels suggest that large arteries respond to both reflex stimuli and changes in blood flow.

Heistad et al1 reported that immersion of the face in water (simulated diving) in humans caused a decrease in forearm blood flow and a significant pressure gra-

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Measurements

of blood flow. Hintze and Vatner used sonomicrometers to measure changes in large coronary artery diameter in dogs during increased blood flow induced by brief (5–20 seconds) periods of coronary occlusion. Increased flow after occlusion caused significant dilation of the artery. Importantly, the "reactive dilation" was observed even when the artery was occluded distal to the site of diameter measurement. Further, dilation after release of occlusion was not observed if postocclusion blood flow was held at control levels by a distal hydraulic occluder. These investigators concluded that the reactive dilatation was flow mediated. Lie et al. reported that increasing femoral artery flow in dogs by means of a distal arteriovenous shunt caused femoral artery dilatation. This dilatation was independent of α- and β-adrenergic receptor and cholinergic mechanisms.

In this study, a dual-crystal pulsed Doppler system was used to measure brachial artery diameter and flow in normal humans. Specific goals of this study were to determine 1) whether or not changes in blood flow produce changes in diameter of the brachial artery independent of changes in local distending pressure and 2) whether or not reflex stimuli produce constriction of the brachial artery that is independent of changes in flow.

Subjects and Methods

Subjects

We studied 23 men and six women with a mean age of 24.1 ± 7 years (range, 20–34 years). None was hypertensive. The studies were approved by the Institutional Committee on Human Investigations, and all subjects gave written, informed consent.

Physiologic Measurements

General. Heart rate was recorded by an electrocardiograph. Blood pressure was recorded each minute by an automatic sphygmomanometer (Life Stat 200, Physio Control, Redmond, Washington). In three experiments, brachial artery pressure was measured directly with a single lumen arterial catheter (Model CPMS400, Cook, Bloomington, Indiana) inserted percutaneously with local anesthetic. Brachial artery diameter and flow velocity were measured in the left arm with the Echovar Doppler System (Model F8C, Alvar Electronics, Chicago, Illinois).

Echovar Doppler system. The Echovar is an 8-MHz range-gated pulsed Doppler system that uses two crystals, both of which transmit and receive, mounted at a 120° angle in a probe. This mounting configuration, developed by Levenson et al., Chauveau et al., and Safar et al., makes it possible to orient the probe so that the emitted signals from both probes cross the vessel at 60°. This permits precise measurement of flow velocity and diameter in large peripheral arteries.

Diameter was measured by emitting a 1-μsec pulse and increasing the depth of measurement until a Doppler-shifted frequency was first detected at the proximal wall of the brachial artery. The pulse was advanced in 0.5-μsec steps across the artery, which yielded a velocity profile within the artery. The last step at which a Doppler-shifted frequency was detected represented the distal wall of the artery. Diameter in millimeters was calculated as N×0.4 mm×0.866 (N=number of steps across the vessel, 0.4 mm=width of a 0.5-msec step, and 0.866=the sine of 60° or the angle at which the beam crosses the vessel).

Mean flow velocity was determined by increasing the volume sampled to encompass the vessel lumen. The Doppler shift then reflects mean flow velocity (V) in the vessel. After determining diameter and mean velocity, flow in milliliters per minute was calculated by the formula π×D²/4×V×60.

The Echovar has been extensively validated in vitro and in vivo. In the present study, reproducibility of diameter and velocity measurements was determined by correlating consecutive measurements made within a study. The correlations between consecutive measurements of brachial artery diameter and velocity within a study were +0.97 (intercept=0.03, slope=+0.93) and +0.78 (intercept=1.4, slope=+0.90), respectively (n=62).

Interventions

Distal circulatory arrest and reactive hyperemia. Blood flow through the brachial artery was altered with an occluding cuff placed on the forearm approximately 8 cm distal to the site of brachial artery measurement. By inflating the cuff to suprasystolic levels (200 mm Hg), the distal circulation (distal circulatory arrest) was arrested, and flow was reduced through the brachial artery measured proximal to the cuff. By deflating the cuff after 10 minutes of inflation, flow was increased through the brachial artery proximal to the cuff (reactive hyperemia).

Reflex stimuli. Changes in brachial artery diameter and flow velocity were measured during the cold pressor test and simulated orthostatic stress with lower-body negative pressure (LBNP). The cold pressor test (CPT) consisted of submerging the contralateral hand up to the wrist in iced water.
LBNP at -20 mm Hg was created by enclosing the lower body in a vacuum chamber sealed at the waist. LBNP pools blood in veins in lower extremities and pelvis and thereby decreases venous return and produces baroreceptor-mediated vasoconstriction. LBNP at -20 mm Hg was used because it decreases forearm blood flow but not mean arterial pressure.10

**Epinephrine infusion.** Brachial artery diameter and flow velocity were measured in the left arm before and during a 30-minute infusion of epinephrine (1.5 μg/min, 45 μg/total dose) into the right antecubital vein. Measurements during infusion were made after heart rate and blood pressure increases had stabilized. This dosage of epinephrine was chosen because studies in our laboratories have shown that it produces significant increases in systolic arterial pressure, heart rate, and forearm blood flow and significant decreases in diastolic arterial pressure.

**Protocols**

*All studies.* Subjects were studied in the supine position after 10 minutes of rest. Room temperature was maintained between 26° and 28° C. The left arm was supported at midthoracic level. The Echovar probe was held stable with a stereotaxic device over the left brachial artery approximately 2 cm proximal to the antecubital fossa.

The brachial artery was located by emitting a long-duration pulse and positioning the probe until it was perpendicular to the brachial artery. Criteria for assuring perpendicular positioning of the probe include 1) the depth at which flow was first detected from the proximal vessel wall was the same on both crystals; 2) similar diameter measurements with both crystals; and 3) similar instantaneous pulse wave forms and mean velocity measurements with both probes. Vessel diameter was measured as described above. Diameter measurements were repeated until consecutive measurements varied by 0.04 mm or less. Flow velocity was measured by increasing the sample volume to encompass the entire vessel lumen. Flow velocity was averaged across 10 cardiac cycles.

**Protocol 1.** Flow-mediated changes were determined by measuring brachial artery diameter and flow velocity in the control state and during arrest of forearm circulation distal to the measurement site (distal circulatory arrest: low flow state). The distal occluding cuff was released after 10 minutes (reactive hyperemia: high flow state). Flow velocity was measured during the first 20 seconds of reactive hyperemia and diameter during the next 90 seconds.

Reflex responses were determined by measuring brachial artery diameter and flow velocity in the control state and during application of LBNP (-20 mm Hg) and the CPT.

**Protocol 2.** These studies were performed to determine whether or not changes in artery diameter during distal circulatory arrest and reactive hyperemia could be explained by a systemic reflex or circulation of ischemic metabolites. Both would be expected to change brachial artery diameter in the contralateral arm. Therefore, brachial artery diameter and flow velocity were measured in the left arm while distal circulatory arrest and reactive hyperemia were performed in the right arm.

**Protocol 3.** These studies were performed to determine whether or not distal circulatory arrest and reactive hyperemia cause substantial changes in local brachial artery distending pressure by altering the pressure gradient across the brachial artery. Changes in local distending pressure were determined directly with an arterial catheter inserted into the brachial artery at the antecubital fossa (distal to the site of diameter measurement) and threaded proximally until positioned approximately at the site of diameter and flow-velocity measurements. Arterial pressure was recorded for 1 minute during control and during the 1st minute of distal circulatory arrest and reactive hyperemia.

**Protocol 4.** To determine whether or not LBNP and the CPT caused constriction independent of reductions in blood flow, brachial artery diameter and flow velocity were first measured in the control state and during distal circulatory arrest. Subsequently, either LBNP or the CPT was applied during distal circulatory arrest. By maximally reducing blood flow with previous distal circulatory arrest, flow-mediated influences on artery diameter were eliminated.

**Protocol 5.** These studies were performed to determine whether or not the elevation in circulating epinephrine levels caused by the CPT11,12 could be the cause of constriction of the brachial artery during the CPT. Brachial artery diameter and flow velocity were measured in the left arm before and during a 30-minute infusion of epinephrine (1.5 μg/min, 45 μg/total dose) into the right antecubital vein. Measurements during infusion were made after heart rate and blood pressure increases had stabilized.

**Statistical Analysis**

Statistical analyses were performed with a repeated-measures analysis of variance. An α level of 0.05 was considered statistically significant. Results are expressed as mean ± SEM.

**Results**

**Flow-Mediated Dilation**

Changes in brachial artery diameter induced by altering blood flow through the brachial artery were studied in 16 subjects. In the control state, brachial artery diameter was 4.74±0.17 mm, flow velocity was 10.9±1.5 cm/sec, and blood flow was 123±20 ml/min. Distal circulatory arrest reduced brachial artery blood flow to 21±5 ml/min (p<0.005) and flow velocity to 2.2±0.4 cm/sec (p<0.001). The reduction in blood flow during distal circulatory arrest was associated with reduction in brachial artery diameter to 4.35±0.20 mm (p<0.001, Figures 1 and 2). Mean arterial pressure (Figure 2) did not change significantly during circulatory arrest.
Systolic and diastolic pressures were 117±2 and 64±2, respectively, during control and 117±2 and 63±2 mm Hg, respectively, during circulatory arrest (NS vs. control).

Deflation of the occluding cuff after 10 minutes (reactive hyperemia) increased brachial artery blood flow to 358±55 ml/min (p < 0.001 vs. control state) and flow velocity to 27.9±3.2 cm/sec (p < 0.001 vs. control state). The increase in blood flow during reactive hyperemia was associated with an increase in brachial artery diameter to 5.6±0.19 mm (p < 0.001 vs. control state, Figures 1 and 2). Mean arterial pressure (Figure 2) did not change significantly during reactive hyperemia. Systolic and diastolic pressures were 117±2 and 64±2, respectively, during control and 117±3 and 62±2 mm Hg, respectively, during reactive hyperemia (NS vs. control).

To exclude systemic reflexes or humoral factors as mechanisms for the changes in brachial artery diameter during distal circulatory arrest and reactive hyperemia, brachial artery diameter and flow were measured in the left arm of seven subjects while circulatory arrest and reactive hyperemia were performed in the right arm. Distal circulatory arrest and reactive hyperemia in the right arm did not change flow, flow velocity, or diameter in the left arm.

To determine whether or not a local brachial artery distending pressure changed during distal circulatory arrest and reactive hyperemia, brachial artery pressure at the site of diameter measurement was recorded directly by arterial cannulation in three subjects. Distal circulatory arrest changed mean brachial artery pressure by −1, +5, and +6 mm Hg in the three subjects. Pulse pressure with distal circulatory arrest changed by +17, −6, and −1 mm Hg in the three subjects. Thus, the brachial artery constricted during distal circulatory arrest despite small and inconsistent changes in local distending pressure. Reactive hyperemia changed mean brachial artery pressure by −5, +7, and +8 mm Hg, respectively, in the three subjects. Pulse pressure with reactive hyperemia changed by −8, +3, and −1 mm Hg in the three subjects. Therefore, the brachial artery dilated during reactive hyperemia despite similarly small and inconsistent changes in local distending pressure.

**Reflex Stimuli**

Changes in brachial artery diameter and flow were measured in 17 subjects during LBNP at −20 mm Hg.

**Figure 1.** Velocity profile across the brachial artery, brachial artery diameter, flow velocity, and flow and mean blood pressure from one subject. Values are shown during control, distal circulatory arrest, and reactive hyperemia. During circulatory arrest, a reduction in velocity and flow occurred. This was accompanied by a reduction in brachial artery diameter. Conversely, velocity and flow increased during reactive hyperemia. This increase was accompanied by an increase in brachial artery diameter.

**Figure 2.** Plot of brachial artery diameter and flow during control and both low (distal circulatory arrest) and high flow (reactive hyperemia) states. Control is resting diameter and flow. Distal circulatory arrest significantly reduced flow (p < 0.005). This was associated with a significant reduction in diameter (p < 0.001). Deflation of the cuff after 10 minutes (reactive hyperemia) significantly (p < 0.001) increased flow and diameter. Values for mean arterial pressure (MAP) are shown at the bottom of the graph. Note that mean arterial pressure did not change significantly during these interventions.
LBNP reduced brachial artery flow from 148±27 to 82±23 ml/min (p < 0.001, Figure 3) and flow velocity from 12.9±1.8 to 7.5±1.6 cm/sec (p < 0.001). LBNP reduced brachial artery diameter from 4.71±0.16 to 4.42±0.18 mm (p < 0.001). Mean arterial pressure did not change significantly during the LBNP (Figure 3). Systolic and diastolic pressures were, respectively, 118±3 and 61±2 during control and 112±3 and 59±2 during LBNP. The 6 mm Hg decrease in systolic pressure was significant (p < 0.01).

Changes in brachial artery diameter and flow were measured in 15 subjects while a CPT was performed in the contralateral arm. As shown in Figure 4, the CPT reduced brachial artery flow from 126±22 to 45±8 ml/min (p < 0.001) and flow velocity from 10.2±1.4 to 4.7±0.6 cm/sec (p < 0.001). The CPT reduced brachial artery diameter from 4.94±0.18 to 4.38±0.18 mm (p < 0.001). In contrast to LBNP, the CPT increased mean arterial pressure from 77±2 to 94±4 mm Hg (p < 0.001). Systolic and diastolic pressures increased from 113±3 and 59±2, respectively, during control to 129±4 and 76±4 mm Hg, respectively, during the CPT (p < 0.001 for both).

LBNP and the CPT reduced blood flow through the brachial artery. Therefore, the observed reduction in brachial artery diameter may be partly “flow-mediated regulation” as well as a result of direct sympathetic constriction of the large artery. To determine whether or not constriction with reflex stimuli was greater than could be explained by reduced blood flow alone, the change in diameter was divided by the change in flow. Figure 5 shows these ratios for distal circulatory arrest, LBNP and the CPT. The ratios of diameter change to flow change were similar for circulatory arrest and LBNP. In contrast, the CPT caused a significantly (p < 0.05) greater change in diameter for a change in blood flow than did distal circulatory arrest or LBNP.

We directly evaluated the contribution of reduced blood flow versus direct sympathetic constriction during the reflex stimuli by performing LBNP and the CPT during distal circulatory arrest. Because neither LBNP nor the CPT could reduce blood flow through the brachial artery beyond that achieved by distal circulatory arrest, we reasoned that constriction observed during circulatory arrest could not be explained by changes in flow and should, therefore, reflect direct sympathetic constriction.

In 13 subjects, distal circulatory arrest previous to LBNP reduced flow (from 105±22 to 24±6 ml/min, p < 0.02), flow velocity (from 9.5±1.6 to 2.4±0.4 cm/sec, p < 0.001) and brachial artery diameter (from 4.67±0.20 to 4.37±0.24 mm, p < 0.005). Applying LBNP during distal circulatory arrest did not further reduce flow (24±6 during distal circulatory arrest vs. 21±59 ml/min during distal circulatory arrest plus LBNP) or flow velocity (2.4±0.6 during distal circulatory arrest vs. 2.2±0.2 during distal circulatory arrest plus LBNP). Importantly, LBNP during distal circulatory arrest did not further constrict the brachial artery (4.37±0.24 during
distal circulatory arrest vs. 4.27 ± 0.22 mm during distal circulatory arrest plus LBNP). Thus, LBNP did not constrict the brachial artery when flow did not change.

In seven subjects, distal circulatory arrest previous to the CPT reduced flow (from 121 ± 28 to 22 ± 2 ml/min, p < 0.01), flow velocity (from 8.8 ± 1.5 to 2.2 ± 0.3 cm/sec, p < 0.005) and brachial artery diameter (from 5.21 ± 0.21 to 4.73 ± 0.18 mm, p < 0.01). The CPT performed during distal circulatory arrest did not further reduce blood flow (22 ± 2 during distal circulatory arrest vs. 21 ± 3 ml/min during distal circulatory arrest plus CPT) or flow velocity (2.2 ± 0.3 during distal circulatory arrest vs. 2.5 ± 0.4 cm/sec during distal circulatory arrest plus CPT). However, in contrast to LBNP, the CPT performed during circulatory arrest did further constrict the brachial artery (4.73 ± 0.18 during distal circulatory arrest vs. 4.36 ± 0.22 mm during distal circulatory arrest plus CPT, p < 0.005).

The CPT raises circulating epinephrine levels. To determine whether or not increases in circulating epinephrine levels could have been the cause of constriction of the brachial artery during the CPT, brachial artery diameter and flow were measured in three subjects before and during a 30-minute infusion of epinephrine at 1.5 μg/min. Epinephrine increased heart rate by +8, +13, and +3 beats/min and mean arterial pressure by +1, −5, and 0 mm Hg in the three subjects. Brachial artery flow increased slightly (+4, +20, and +17 ml/min). Epinephrine infusion did not change brachial artery diameter (0, −0.09, and 0 mm). Thus, epinephrine did not constrict the brachial artery.

**Flow Compared With Velocity**

Flow is calculated from diameter and velocity and is, therefore, not independent of diameter. Therefore, we also analyzed changes in brachial artery diameter as a function of changes in velocity (velocity data are reported above). In all cases, analysis of diameter changes as a function of velocity changes yielded results similar to those derived from relating diameter to flow.

**Discussion**

The distinctive feature of this study was the direct measurement of brachial artery diameter in humans during altered flow states and reflex stimuli. There were two principal findings. First, the alteration of flow through the brachial artery was associated with changes in diameter. Specifically, decreasing blood flow below control levels caused a reduction in brachial artery diameter, whereas increasing blood flow caused an increase in brachial artery diameter. These results strongly suggest flow-mediated regulation of large artery diameter. Second, reflex stimuli (LBNP and the CPT) caused brachial artery constriction. Brachial artery constriction with LBNP did not exceed that which could be explained by a reduction in blood flow through the brachial artery secondary to reflex constriction of small downstream vessels.

In contrast, brachial artery constriction with the CPT exceeded that which could be explained by reduced flow alone and presumably reflected direct sympathetic constriction of the brachial artery. The discussion will consider flow-mediated dilatation, responses to reflex stimuli, and evidence that flow-mediated dilatation is active at normal physiologic flow levels.

**Flow-Mediated Dilatation**

Distal circulatory arrest and reactive hyperemia were used to alter flow through the brachial artery. These interventions did not change mean systemic arterial pressure and would seem to indicate flow-mediated regulation of brachial artery diameter. However, we considered three alternative explanations of the results.

First, distal circulatory arrest and reactive hyperemia may alter the pressure gradient from the aorta to the brachial artery and change local distending pressure. Specifically, distal circulatory arrest decreases flow and may reduce the gradient (increasing local brachial artery distending pressure), whereas reactive hyperemia increases flow and may increase the gradient (reducing local brachial artery distending pressure). However, the pressure gradient across the brachial artery is small under control conditions (approximately 4 mm Hg). Further, Melkumyants et al13 have reported that the dilatation induced by increasing flow through feline arteries compensated for the increased flow and resulted in little change in distending pressure across the arteries. Finally, with intra-arterial recordings of brachial artery distending pressure in the present study, we demonstrated that distal circulatory arrest produced only small and inconsistent increases in brachial artery distending pressure. Reactive hyperemia caused only small and inconsistent decreases in brachial artery distending pressure. Therefore, changes in brachial artery diameter during distal circulatory arrest and reactive hyperemia cannot be attributed to passive changes in vascular caliber secondary to changes in distending pressure.

Moreover, it is highly improbable that the changes in brachial artery diameter during altered flow were caused by myogenic autoregulation. The changes in distending pressure were small, and large arteries reportedly do not exhibit substantial myogenic responses. Thus, changes in brachial artery diameter during distal circulatory arrest and reactive hyperemia cannot be explained on the basis of changes in distending pressure.

Second, we considered the possibility that systemic circulation of ischemic metabolites may cause brachial artery dilatation during reactive hyperemia. This seems unlikely because dilatation was not observed when reactive hyperemia was performed in the contralateral arm. Lie et al6 also have reported that release of ischemic metabolites failed to cause dilatation of the femoral artery in the contralateral leg in dogs. Thus, systemic circulation
of humoral factors would not seem to account for dilatation of the brachial artery during reactive hyperemia.

Third, we considered the possibility that distal circulatory arrest and reactive hyperemia might have altered brachial artery diameter by perturbing cardiovascular reflexes. Circulatory arrest and reactive hyperemia did not, however, alter heart rate, systemic arterial pressure, or brachial artery diameter measured in the contralateral arm. A venoarterial axon reflex elicited by venous distension could potentially be involved in brachial artery responses during distal circulatory arrest and reactive hyperemia. However, this seems unlikely because such reflexes are local and would not be expected to extend to the brachial artery 5 cm proximal to the site of circulatory arrest or reactive hyperemia. Further, reactive hyperemia causes venous distension but dilates the brachial artery. In addition, other studies have demonstrated flow-mediated dilatation in arteries transected several centimeters distal to the site of diameter measurements. Finally, Hintze and Vatner have shown that flow-mediated dilatation is not altered by combined α- and β-adrenergic receptor blockade or ganglionic blockade. Thus, neither systemic nor local reflexes are likely explanations for the changes in brachial artery diameter during distal circulatory arrest and reactive hyperemia.

Reflex Stimuli

Both LBNP and the CPT caused constriction of the brachial artery. Brachial artery constriction during these reflex stimuli could reflect 1) direct sympathetic constriction of the brachial artery; 2) flow-mediated regulation secondary to decreases in brachial artery flow from sympathetic constriction of small downstream vessels; and 3) myogenic constriction secondary to increases in brachial artery pressure, particularly during the CPT.

Because both reflex stimuli reduced blood flow, constriction of the brachial artery during these interventions could be explained at least in part by the reduction in flow rather than a direct sympathetic effect on the artery. Specifically, two findings suggest that the brachial artery constriction associated with LBNP was flow-mediated. First, the change in diameter for unit change in blood flow with LBNP was not greater than that found with distal circulatory arrest, a stimulus that constricts the brachial artery solely by decreasing flow. Second, LBNP performed during distal circulatory arrest did not further constrict the brachial artery. Thus, when LBNP did not reduce brachial artery flow, it did not cause brachial artery constriction. These observations suggest that LBNP constricts small vessels primarily and that its effect on brachial artery diameter is secondary to reduced flow through the brachial artery rather than direct sympathetic constriction.

In contrast to LBNP, the data suggest that brachial artery constriction during the CPT cannot be explained solely by a decrease in brachial artery flow. First, the change in diameter for unit change in flow was significantly greater with the CPT than with distal circulatory arrest. Second, the CPT performed during distal circulatory arrest caused brachial artery constriction despite the fact that brachial artery flow did not change. These findings suggest direct sympathetic constriction of the brachial artery during the CPT. This could reflect neurogenic sympathetic constriction of the brachial artery or, conceivably, sympathetic constriction secondary to increases in circulating epinephrine that are reported to occur during the CPT. However, we did not observe constriction of the brachial artery during infusion of epinephrine in three subjects, and therefore, we suggest that the sympathetic constriction of the brachial artery during the CPT is probably neurogenic and not humoral.

The CPT increased mean arterial pressure significantly. This increase in pressure may produce myogenic constriction of the brachial artery. It seems improbable, however, that a myogenic response would cause the brachial artery to constrict below control diameter, particularly because large arteries reportedly do not exhibit substantial myogenic responses. Further, Lie et al reported that an increasing large artery distending pressure causes passive dilatation and not myogenic constriction. They varied perfusion pressure in the femoral artery of anesthetized dogs and found that artery diameter varied in proportion to blood pressure. Thus, a myogenic response does not seem a plausible mechanism for the brachial artery constriction we observed during the CPT.

Physiologic Mechanisms and Significance

Studies of canine arteries by Pohl et al and Holtz et al and of feline arteries by Melkumyants et al have suggested that flow-mediated dilatation is tonically active at physiologic flow levels. The present study provides evidence for tonically active flow-mediated dilatation of a large peripheral artery in humans. First, distal circulatory arrest reduced flow and brachial artery diameter. The reduction in flow with distal circulatory arrest exceeded physiologic levels and does not, therefore, indicate whether or not flow-mediated dilatation is tonically active within normal flow variations. However, LBNP at ~20 mm Hg, a baroreflex stimulus that mimics normal flow variations during orthostatic stress, also reduced flow and caused brachial artery constriction. The reduction in brachial artery diameter with LBNP appears to represent flow-mediated regulation. These results suggest that flow-mediated dilatation is tonically active at normal flow rates and participates in regulation of large arteries during physiologic states in humans.

Although this study is, to our knowledge, the first to demonstrate systematically flow-mediated changes in large peripheral artery diameter in humans, it is not the first to measure brachial artery diameter
during changes in flow in humans. Levenson et al\textsuperscript{18} measured changes in brachial artery diameter during occlusion of blood flow to the hand with a wrist occluding cuff. Wrist occlusion reduced blood flow and caused a nonsignificant reduction in brachial artery diameter. The findings of Levenson et al\textsuperscript{18} are not inconsistent with the present study because wrist occlusion did not decrease brachial artery flow to the degree achieved by arresting forearm circulation in our study.

This study did not address the role of the endothelium in flow-mediated dilatation. There is considerable evidence, however, that the endothelium is importantly involved in flow-mediated dilatation.\textsuperscript{16,17,19,20} Based on studies of isolated vessels, Holtz et al\textsuperscript{17} proposed that vasodilatation during increased flow is mediated by the endothelium. Pohl et al\textsuperscript{16} subsequently used sonomicrometers to measure in vivo changes in diameter of canine femoral arteries associated with changes in flow. Increasing flow by an arteriovenous shunt or peripheral vasodilatation caused dilatation of the femoral artery. The flow-mediated dilatation was abolished by denuding the endothelium, indicating that endothelial cells mediate flow-dependent dilatation. Hull et al\textsuperscript{21} also reported dilatation of canine femoral and saphenous arteries when flow was increased by an arteriovenous shunt. Rubanyi et al\textsuperscript{22} have shown that increasing flow through canine femoral artery segments causes dilatation. Flow-mediated dilatation was abolished by removal of the endothelium. Although the mechanism of flow-mediated dilatation is unknown, it is thought to involve release of one or more relaxing factors by the endothelium.\textsuperscript{23,24} From our observations, we cannot state whether or not the flow-mediated dilatation that we observed is endothelial dependent.

In conclusion, this study indicates that the tone of large peripheral arteries in humans responds to changes in blood flow. High flow dilates and low flow constricts the brachial artery. Further, this study demonstrates that large arteries participate in peripheral vascular responses to reflex stimuli. Changes in large artery diameter associated with reflex stimuli can be secondary to changes in flow or may reflect direct sympathetic constriction of large arteries.

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