Relationship between blood velocity and conduit artery diameter and the effects of smoking on vascular responsiveness

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Stoner, Lee, Manning Sabatier, Kristy Edge, and Kevin McCully. Relationship between blood velocity and conduit artery diameter and the effects of smoking on vascular responsiveness. J Appl Physiol 96: 2139–2145, 2004. First published January 16, 2004; 10.1152/japplphysiol.01107.2003.—Transient changes in arterial diameter in response to transient ischemia-induced changes in arterial blood velocity have been used as an index of vascular health. The purpose of this study was to determine the relationship between blood velocity and diameter in the brachial artery by different methods of increasing blood velocity. Acute cigarette smoking was used with otherwise healthy young occasional smokers to determine the influence of endothelial-nitric oxide pathways on the arterial diameter-blood velocity relationship. Nine nonsmokers and 12 occasional smokers (<1 pack/wk) were tested. Blood flow to the forearm was manipulated to indirectly investigate the relationship between blood velocity and diameter in the brachial artery. Blood flow to forearm was manipulated through the use of 1) 5-min ischemia; 2) handgrip exercise; 3) indirect local heating; and 4) 5-min ischemia plus indirect local heating. A strong relationship was observed between blood velocity and diameter independent of the method used to increase blood velocity ($R^2 = 0.89$). The mean slope of the velocity-diameter relationship was not different between nonsmokers and occasional smokers who abstained from smoking at least 2 days. Acute smoking did not alter the slope of the velocity-diameter relationship although the mean intercept was decreased as a result of consistent vasoconstriction (7–10%). The mechanisms by which smoking impairs vascular health are largely unknown. These findings differ from previous smoking studies that used chronic and/or heavier smokers. The velocity-diameter relationship appears independent of the method for increasing velocity. Acute smoking in occasional smokers results in vasoconstriction without altering vascular responsiveness. The velocity-diameter relationship may be a useful measure of the progression of vascular disease.

flow-mediated dilation; vascular reactivity; vascular tone; cigarette smoking

VASCULAR ENDOTHELIAL CELLS play an important role in maintaining cardiovascular homeostasis primarily through the release of protective bioactive substances, the most widely studied being nitric oxide (NO) (29, 34, 41). Releasing NO is not the only function of the endothelium, but the capacity of the endothelium to do this has been recognized as an important surrogate marker of general endothelial health (6, 8, 12). Heart disease, diabetes, hypertension, aging, and smoking, among other factors, have been associated with reduced vascular endothelial-NO function (9–11, 21, 28). In addition, reduced endothelial function has been shown to predict future incidence of cardiovascular disease (42).

Endothelial function has been assessed in humans both invasively and noninvasively. Noninvasive assessments have significant advantages in studying clinical populations. The current standard for noninvasive assessment of vascular health is the flow-mediated dilation (FMD) test (10). This test of vascular vasoreactivity measures the increase in arterial diameter in response to the increase in blood velocity flow typically after 4–5 min of ischemia. The increase in diameter reflects the ability of the endothelium to relax vascular smooth muscle in response to blood velocity-induced increases in shear stress (15). The primary mechanism thought responsible for this vasoactive response is the local release of NO (10, 39). The NO then induces the vascular smooth muscle to relax. On the basis of these results, it might be expected that progressive increases in blood velocity and shear stress should produce dose-dependent changes in arterial diameter. Indeed, previous studies have demonstrated that FMD is related to the duration of ischemia and to the magnitude of hyperemia when measured both as blood flow and peak shear rate (7, 27, 44, 47).

Cigarette smoking is considered a prominent risk factor for cardiovascular disease because it has been shown to promote vascular dysfunction in not only active smokers but also passive smokers (9, 16, 28, 35, 40). Although the precise mechanisms remain unknown, evidence suggests that smoking impairs endothelial function through the production of oxygen-derived free radicals that impair NO biosynthesis (3–5). In chronic smokers after smoking one cigarette, FMD has been shown by using the presmoking baseline diameter to be transiently reduced by ~66% for up to 90 min (28). Acute exposure to cigarette smoking would therefore be expected to attenuate the ability of conduit arteries to vasodilate in response to increased blood velocity flow for a notable period of time. As a known inhibitor of endothelial function, acute smoking may be considered an appropriate choice in assessing the importance of endothelial function in maintaining vascular reactivity as assessed by the relationship between blood velocity-conduit artery diameter.

The purpose of the present study was to evaluate the relationship between blood velocity and brachial artery diameter. The study also aimed to address the importance of endothelial-NO pathways for maintaining this relationship. Although previous studies have used FMD to assess the implications of vascular health risk factors, to our knowledge no study has looked to determine how acute endothelial dysfunction may impair the blood velocity-arterial diameter relationship. Two hypotheses were tested: 1) regardless of the method used for increasing blood velocity, there would be a linear relationship between velocity and diameter; and 2) this relationship would be impaired by acute cigarette smoking in occasional smokers. The present study used 1) reactive hyperemia, 2) progressive-
intensity handgrip exercise, 3) local indirect heating, and 4) reactive hyperemia plus indirect local heating to manipulate blood velocity in vivo.

METHODS

Subjects and study design. A total of 21 healthy and moderately active subjects were recruited for this study. Informed consent was obtained from the subjects after they were given a detailed description of the procedures. The study was approved by the University of Georgia Institutional Review Board.

Nine healthy male and female nonsmokers (20–26 yr old) and 12 otherwise healthy male and female (19–23 yr old) occasional cigarette smokers (reported to smoking ≤1 packet/wk) were required to make two visits to the laboratory. Subjects were excluded from the study if they demonstrated any cardiovascular disease health risks. The nine healthy nonsmokers were used to test for a linear relationship between velocity and diameter and to determine the coefficients of variation (CVs) of diameter and velocity measures. For the nonsmokers, the two study session results were averaged for comparison with the smokers. All the smokers were tested with each study condition without smoking. Seven of the smokers repeated all study conditions after smoking one filtered cigarette (12 mg tar, 1.0 mg nicotine) before each condition (3 cigarettes total). Six smokers only repeated the FMD condition after smoking. The subjects were asked to inhale the smoke and to smoke the entire cigarette. Each testing condition resumed immediately after finishing the cigarette. The smoke group verified that they did not smoke for at least 2 days before reporting to the laboratory for any stage of testing.

For both groups, the test sessions were performed on weekdays starting between the hours of 7 and 11 AM. The two test sessions were completed within 48 h. All subjects were asked to report to the laboratory in the fasted condition, having refrained from exercise for 48 h before testing. Subjects were also asked not to consume caffeine or administer any medications with known vascular actions before testing. All stages of testing were performed in a climate-controlled laboratory setting.

Measurement of blood velocities and vessel diameter. A GE 400CL duplex color Doppler imager (GE Medical) was used to assess diameters of the brachial artery, along with simultaneous measurement of blood velocity (37). All brachial artery diameter and blood velocity measurements were taken in the left arm for all stages of testing. Blood velocity was calculated by using a pulsed Doppler signal angled 45°–60° to the vessel. The operator manually set the Doppler gate to record blood velocity from the proximal to distal wall of the artery. Integrated GE medical software was used to calculate the minimum and maximum velocities and the time-averaged maximum velocity for every heart beat. Pulse pressure was calculated by subtracting minimum from maximum velocities. Blood velocity was recorded in real time via optical character-reading software (Ammons Engineering) specially coded for operation through Labview (National Instruments). High-resolution B-mode imaging with a 5- to 10-MHz linear-array ultrasound transducer was used to measure changes in arterial diameter. All measurements were performed with the same position of the transducer on the arm. Magnification and focal zone settings were adjusted to optimize imaging of the proximal and distal vessel wall. Gain was kept constant throughout. Diameter measurements were taken at end diastole. Brachial artery diameters were measured offline with semiautomated edge-detection software specially coded for use with Labview. Briefly, the operator selected a region of interest along the length of the arterial wall. The true edges of the arterial walls were then represented by a line of best fit located by gradient-based detection within the region of interest. Arterial diameter was then estimated via a least-squared-error model fit.

FMD. After 15 min of rest in the seated position, images of the brachial artery diameter were recorded every 30 s for 5 min during baseline. Blood flow velocity measurements were recorded continu-ously. A pneumatic tourniquet (Hokanson) placed around the left forearm distal to ultrasound measurements was then rapidly inflated (<1 s) to a pressure of ~100 mmHg above systolic blood pressure. Brachial artery images were recorded every 30 s during cuff inflation for 5 min. The pressure was then quickly released from the cuff to induce reactive hyperemia, and brachial artery images were recorded every 3–5 s for 2 min. Consistent with previous studies, the diameter response to reactive hyperemia was measured at a different time point than the peak velocity response (10). Images were then collected every 30 s for an additional 3 min after tourniquet release. Measurements were taken during the last 2 min of recovery were averaged to represent recovery values. Heart rate (Biopac) and blood pressure (Datascope Accutor 3) were measured to account for systemic autonomic influences. A teletethermometer (YSI) was used to record the temperatures of skin covering the surface of the left brachial artery, right brachial artery, and left radial artery every 2 min throughout the study.

Graded exercise. After recording of baseline measures, maximum voluntary contraction force was determined from three trials squeezing a handgrip ergometer. The handgrip ergometer was connected to a Biopac acquisition system using a force transducer interface. After 5 min of rest, repeated rhythmic handgrip exercise was performed at two intensities: 1) 30% maximal voluntary contraction (MVC) and 2) 50% MVC. The mode of exercise was chosen on the basis of pilot work that showed that we could maintain ultrasound imaging during the exercise. The intensities were also chosen because they closely matched the hyperemic response to 40°C and 42°C heated conditions with our pilot work. Exercise consisted of one contraction every 4 s for 4 min. Low- to moderate-intensity handgrip exercise of a small muscle group was chosen to minimize systemic autonomic responses. A three-lead electromyograph (Biopac) was attached to the surface of the left biceps muscle of the subjects to determine the possible confounding influence of biceps muscle contraction. Subjects were encouraged to perform the exercise with minimal activation of the biceps muscle. For the last minute of each exercise stage, brachial artery images were collected every 10–20 s. After the last stage of exercise, a further 5 min of measurement were recorded. The measurement recordings taken from the last 2 min of recovery were averaged.

Indirect local heating. Local heating was used to indirectly increase blood velocity through an artery upstream (the brachial artery) from the area of heating. Warming of the skin is thought to increase blood flow locally without significant systemic autonomic influence (23, 24, 43, 46). The subject’s forearm was then immersed into 40°C water for 5 min of acclimatization before 5 min of data collection. The above procedure was repeated with the forearm immersed in 42°C water. After 5 min of acclimatization at 42°C, 5-min ischemia was repeated followed by 5 min of recovery. Images were recorded every 30 s during cuff inflation for 5 min. Five-minute acclimatization was chosen on the basis of our pilot work, which showed this temperature to provoke a maximal increase in blood velocity through the brachial artery upstream. The 40°C temperature was chosen because we found this temperature to induce an increase in blood velocity halfway between baseline and maximal at 42°C.

Statistical analysis. Blood velocity, brachial artery vasoactive (diameter) responses, blood pressure variables, and heart rate were averaged for each protocol collection period. FMD was expressed as the percent change in brachial artery diameter after reactive hyperemia relative to the average diameter of 5-min baseline.

We had inadequate power to make appropriate gender comparisons within groups. Therefore, to evaluate possible gender interactions, the female subjects from the control (average of 2 days) and smoke groups (nonsmoking day only) were pooled together, and similarly with the men. Baseline diameters and FMD dilation values for men vs. women were compared by using a one-way ANOVA to see whether a gender interaction was evident.
Descriptive data for each stage of testing are expressed as means ± SD for both the control group and smoke group. The reproducibility for the control group brachial diameters and velocities were expressed using CVs. The brachial diameters and blood velocities for the smoking group pre- and postsmoking were compared by use of repeated-measures ANOVA. Heart rates, blood pressure variables, and skin temperature values for each condition were compared by use of two-tailed paired t-tests.

To determine the blood velocity-diameter relationship, mean blood velocity for each condition was correlated against mean diameter size for each condition by using a least squares regression. For the control group, the two trials were averaged together for comparisons against the smoke group on the abstain day. For controls vs. smokers, the intercept, slope, and FMD values between groups were compared by use of a two-tailed independent t-test. A one-tailed paired t-test was used for the smokers pre- to postsmoking. Standardized mean differences (d) are used to represent the size of significant effects. The critical α value for each statistic test was set at 0.05.

RESULTS

Table 1 demonstrates the heart rates and blood pressures for the control and smoking groups for all test sessions. No significant differences for any baseline measures were seen between groups or between trials. Resting heart rate (P = 0.35) and systolic blood pressure (P = 0.24) were higher for the smokers at rest but not significantly because of large group variances. Smoking did not increase heart rate or blood pressures. Skin temperature over the brachial artery was also not different between conditions or trials, except for the 42°C indirect heating condition. With 42°C indirect heating, the skin temperature over the brachial artery was warmer compared with room temperature baseline (P = 0.003). There was no significant difference in brachial area skin temperature between trials for either the control subjects or smoking subjects. However, pooling together both groups (controls plus smokers on abstain day), we found that heart rate was increased above baseline (73 ± 12 beats/min) with exercise (30%MVC = 76 ± 11 beats/min, P = 0.01; 50%MVC = 76 ± 12 beats/min, P = 0.18). Similarly mean arterial pressure increased above baseline (84 ± 8 mmHg) with exercise (30%MVC = 89 ± 10, P = 0.005; 50%MVC = 93 ± 13 mmHg, P = 0.002). Heating had no effect on heart rate or mean arterial pressure.

Women had significantly smaller room temperature baseline diameters (P < 0.001), and there was a trend for greater FMD values than for men, as expected. This finding is consistent with the literature (2, 30). However, smoking decreased room temperature baseline (−3.8 ± 4.54% vs. −7.92 ± 5.34%, P = 0.19) and maximal diameters (−5.13 ± 5.87 vs. −9.28 ± 7.01%, P = 0.292) similarly for women and men, respectively. Thus male and female subjects were combined in subsequent analyses.

Nonsmoking group. Blood velocity increased in response to handgrip exercise, local indirect heating, and ischemia (Fig. 1). Exercise resulted in up to a threefold increase in velocity over resting. Indirect heating produced a similar approximately threefold increase in blood velocity. Reactive hyperemia resulted in an approximately sixfold increase in blood velocity. All three conditions resulted in significant increases in arterial diameter. Table 2 shows representative diameters and velocities, as well as FMD, FMD with heat, intercept, and slope day-to-day means and CV values.

There was a strong positive relationship between blood velocity and arterial diameter for all the conditions. This relationship was consistent over the two trials (day 1, R² = 0.90; day 2, R² = 0.89).

Smoking trials. Before smoking (>2 days of abstinence), the 12 smokers had blood velocity and diameter responses to ischemia, exercise, and indirect heating that were similar to the control subjects (Fig. 1). Seven of the smokers completed all the exercise, ischemia, and indirect heating trials while continuing to smoke throughout the testing. Smoking resulted in a significant 7–10% decrease in diameter for each study condition (Fig. 2), F(1,36) = 48.79, P < 0.001, ω² = 0.58. There was no interaction between conditions and diameter scores, F(5,36) = 0.851, P = 0.52, ω² = 0.11. Smoking had no significant effect on velocities, F(1,36) = 0.303, P = 0.59, ω² = 0.01. Smoking did not alter the mean slope of the velocity-diameter relationship (P = 0.47, d = 0.09) despite decreasing the mean intercept (P = 0.01, d = 0.51). There were no significant differences in slope (P = 0.22) or intercept (P = 0.99) values between controls and smokers under nonsmoking conditions (n = 12).

Smoking one cigarette resulted in a significant decrease in room temperature FMD (n = 12, P = 0.03, d = 1.21, see Fig. 3). This was based on using the initial nonsmoking diameter as the baseline. If the resting diameter after smoking was used as the baseline, no impairment in room temperature FMD was seen (P = 0.35). FMD was also not significantly different between controls and smokers when not smoking (P = 0.62).

DISCUSSION

This study found a strong linear relationship between peak blood velocity and arterial diameter in the brachial artery. Our results are consistent with a previous study showing varying

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Table 1. Heart rate and blood pressures for control and smoking groups for all test sessions

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th>Smoke Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trial 1</td>
<td>Trial 2</td>
</tr>
<tr>
<td>n</td>
<td>9 (5 men/4 women)</td>
<td>12 (8 men/4 women)</td>
</tr>
<tr>
<td>Age, yr</td>
<td>22.7±2.9</td>
<td>23.4±2.5</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>68.9±12.1</td>
<td>68.1±12.8</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>110±15.5</td>
<td>114±6.6</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>63.6±6.4</td>
<td>64.8±5.7</td>
</tr>
<tr>
<td>Mean BP, mmHg</td>
<td>83.0±10.1</td>
<td>84.2±8.5</td>
</tr>
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</table>

Values are means ± SD. BP, blood pressure.

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durations of ischemia produce a consistent velocity-diameter relationship (27). An additional study used distal and proximal tourniquet-induced ischemia with and without finger flexion exercise to manipulate the hyperemic response (7). The investigators found arterial diameter to be related to peak forearm blood flow. In our study, a linear velocity-diameter relationship was seen even though we used very different methods to increase blood velocity, including reactive hyperemia, exercise, and indirect heating. By using several different velocity conditions, we were able to calculate a slope of the velocity-diameter relationship. The slope of this velocity-diameter relationship has the potential to serve as a sensitive measure of vascular responsiveness to velocity.

The between-days CVs in the diameter measurements in our study were 2.0–3.0%, consistent with the literature (1). However, the CV for FMD (~28%) was much larger. Our CV value according to a recent review by De Roos et al. (12) is comparable to those found in the literature. Some studies have found much lower CV values, but De Roos et al. suggested that CVs for FMD in these studies were calculated incorrectly and that CV for FMD calculated in their study was 50% for six trials. The CV for intercept of velocity-diameter correlations was <4%, whereas CV for slope was similar to FMD at 29%. Some of the CV for the slope may be attributable to velocity.

Despite similar day-to-day mean velocity values, CVs were higher for velocities (~15–31%) than for diameters. The use of peak velocities postischemia measured with only one point may introduce variance such as variations in blood flow with the respiratory cycle. We feel that we eliminated as far as possible the error variance associated with transient increases in velocity and diameter, supported in part by lower CV values during the conditions in which we were able to control increases in blood velocity (i.e., heat and exercise).

We chose to use blood velocity as our independent variable. However, vasodilation is thought to be mediated through the level of shear stress on the vessel wall. Increases in shear stress are thought to stimulate vascular endothelial cells to release vasoactive substances, including NO and prostacyclin, with NO thought of as most potent (15, 26, 39). We decided not to calculate shear stress because of uncertainties regarding the velocity profile and the presence of turbulence. We do not feel that presenting our data as velocities rather than calculated shear stresses significantly influenced the interpretation of our results. Indeed, previous studies have demonstrated that peak velocity accurately predicts shear stress (44) and that both blood flow and shear stress predict FMD (17). Interestingly, we did find that the time-averaged maximum blood velocity produced a stronger linear relationship with diameter than our other measures of velocity, including \( V_{\text{max}} \) during systole and pulse velocity (difference between systolic and diastolic velocities) (data not shown).

This study was limited in that we were unable to determine the mechanisms by which increases in velocity increased diameter size. However, we saw a strong velocity-diameter relationship even though each of our protocols may have increased velocity by different mechanisms. Numerous previous studies have suggested dilation in response to ischemia-induced reactive hyperemia is primarily endothelial-NO dependent (10, 15, 39). However, ischemia-induced reactive hyperemia results in only transiently increased blood velocities. With handgrip exercise and heating we achieved increases in velocity that were stable before making diameter measurements. Both of these protocols increased blood flow demand.

### Table 2. Representative diameters and velocities and FMD, FMD with heat, intercept, and slope day-to-day means and CV values

<table>
<thead>
<tr>
<th>Variable</th>
<th>( n )</th>
<th>Day 1</th>
<th>Day 2</th>
<th>CV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base diameter, cm</td>
<td>16</td>
<td>0.39±0.08</td>
<td>0.39±0.08</td>
<td>2.7</td>
</tr>
<tr>
<td>Maximum diameter, cm</td>
<td>16</td>
<td>0.43±0.07</td>
<td>0.43±0.08</td>
<td>2.4</td>
</tr>
<tr>
<td>Base velocity, cm</td>
<td>16</td>
<td>0.17±0.10</td>
<td>0.19±0.11</td>
<td>30.8</td>
</tr>
<tr>
<td>Maximum velocity, m/s</td>
<td>16</td>
<td>1.07±0.23</td>
<td>1.11±0.53</td>
<td>14.6</td>
</tr>
<tr>
<td>FMD, %</td>
<td>16</td>
<td>10.2±5.03</td>
<td>10.0±4.03</td>
<td>27.9</td>
</tr>
<tr>
<td>Heat + FMD, %</td>
<td>12</td>
<td>18.2±8.57</td>
<td>16.9±4.38</td>
<td>32.8</td>
</tr>
<tr>
<td>Intercept</td>
<td>12</td>
<td>0.39±0.09</td>
<td>0.39±0.08</td>
<td>3.6</td>
</tr>
<tr>
<td>Slope</td>
<td>12</td>
<td>0.05±0.01</td>
<td>0.05±0.01</td>
<td>29.1</td>
</tr>
</tbody>
</table>

Values are means ± SD. FMD, flow-mediated dilation; CV, coefficient of variation.
downstream from the brachial artery but may have done so by recruiting different mechanisms. Previously it has been suggested that FMD with proximal occlusion may be less NO pathway dependent (14) than distal occlusion but that FMD with proximal occlusion is actually more predictive of cardiovascular disease than FMD with distal occlusion (47). Despite the potential for more than one mechanism being involved, we feel that vascular responsiveness remains a potentially valid marker of vascular function and health.

Although we had inadequate power to accurately determine gender interactions, we did see similar responses in men and women to each condition pre- and postsmoking. Previously it has been recognized that differences between female and male vascular responsiveness exist (20). We did see a trend for women to have smaller baseline diameters and larger FMD values. However, it has been shown that the smaller initial diameters in women result in larger increases in mean shear stress with increased velocity (22). We feel that the use of the velocity-diameter relationship may negate such limitations of using FMD alone, although also we agree that gender may play a more prominent role in aging and pathology.

We chose to use cigarette smoking as an intervention for assessing the role of NO pathways in the velocity-diameter relationship because previous studies demonstrate that smoking impairs endothelial-NO function (9, 16, 28, 35, 40). Interestingly, smoking did not alter the slope of the velocity-diameter relationship. It is possible that smoking did impair NO pathways but that in otherwise healthy young smokers other mechanisms may compensate. Another possible explanation is that a functional NO reserve may exist. A recent study demonstrated that salt loading reduced NO production in healthy subjects without reducing NO-mediated vasodilation (13). Additionally, our exercise and heating conditions may have recruited mechanisms that were different from, or in addition to, endothelial-NO dependent vasodilation.

Previous studies have shown that acute cigarette smoking impairs FMD by as much as 60–70% (9, 28, 32, 35) in regular smokers, suggesting decreased vascular function. One explanation for the differences between our results and previous studies is the choice of baseline diameters used to calculate FMD. At least one previous study has shown that the absolute change in diameter pre- to postsmoking is unchanged when using the baseline immediately postischemia (i.e., postsmoking baseline) is used (45). As shown in Fig. 3, using the initial presmoking baseline as the reference for calculation resulted in FMD impairment of 79%, consistent with previous studies. However, when using the postsmoking resting diameter to calculate FMD we found no effect of acute smoking on FMD, consistent with Stadler et al. (45). Notably, our occasional smokers also did not have reduced FMD relative to nonsmoking subjects when they had not smoked in 2 days. This is not consistent with previous studies (9, 28, 35). However, these previous studies generally used older subjects with a heavier smoking history. Our subjects’ low smoking level along with their young age suggests that they might have minimal chronic effects. Thus we feel our results are consistent with previous studies if smoking-induced vasoconstriction and smoking history are taken into account. However, the result we found with young occasional smokers may not be extrapolated to older chronic smokers.
Although smoking did not reduce the slope of the velocity-diameter relationship, there was a significant decrease in the intercept. Smoking resulted in a 7–10% decrease in arterial diameter at rest and during all subsequent conditions. This magnitude of constriction with smoking is consistent with previous studies (28, 32, 45). This finding suggests that acute smoking increases vascular tone. Tone is partly governed by basal levels of NO bioavailability (19, 25, 38), i.e., the greater the NO levels the lower the resting tone. Thus smoking may have increased tone through its effects on NO bioavailability. If so, this would suggest tone to be more greatly influenced by NO than vascular reactivity. Another explanation is that smoking increased vascular tone through increased sympathetic nervous system (SNS) activity (18, 19, 31, 36, 38). We did not measure SNS directly, and we realize this would have been a potentially useful measurement to make. The absence of change in heart rate or blood pressure with smoking suggests SNS activity was unaltered, although changes in SNS activity can occur independent of changes in central hemodynamic markers (18).

Our findings suggest that noninvasive measures of vascular function such as FMD require careful interpretation. There has been much debate as to the best tool for screening vascular pathology and assessing the impact of vascular health risk factors. This study suggests that attention is also warranted as to how widespread and known potent cardiovascular disease risk factors such as smoking interact with vascular function to promote the course of pathology. The use of a simplified method for measuring the vascular responsiveness of conduit arteries to velocity may help to determine the effects of acute and chronic vascular health risk factors. This finding is potentially useful in that it may help identify the pattern of vascular dysfunction with pathology.

In summary, brachial artery diameter demonstrated a linear relationship with blood velocity independent of the method used for increasing velocity, including ischemia, exercise, indirect local heating, and indirect local heating plus ischemia. This suggests that vascular responsiveness can be measured as the slope of the velocity-diameter relationship. Acute cigarette smoking resulted in a consistent 7–10% decrease in arterial diameter for each condition but did not alter the slope of the velocity-diameter relationship, suggesting that acute smoking increased vascular tone independent of vascular responsiveness in young occasional smokers. The interpretation of these results may be limited to those exposed to occasional cigarette smoke, but this is a sizeable portion of our society. This study demonstrates a need to better understand the relationship between NO pathways, vascular tone, and vascular responsiveness and demonstrates the need for careful interpretation of in vivo vascular health tests. The methods used herein may help to expand our understanding of vascular pathology.

**REFERENCES**


**GRANT**

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