

# A comparison between active- and reactive-hyperaemia-induced brachial artery vasodilation

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## A B S T R A C T

The measurement of brachial artery vasodilation in response to a hyperaemic stimulus has been used extensively to assess changes in endothelial function. However, whether or not similar changes occur in response to an active hyperaemic stimulus is unknown. The purpose of the present study was to compare brachial artery vasodilation in response to an active compared with a reactive hyperaemic stimulus following a known perturbation of endothelial function. Eight apparently healthy adults were assigned to four treatment conditions in a counter-balanced design: (i) low-fat meal with active hyperaemic stimulus (LFM-A), (ii) high-fat meal with active hyperaemic stimulus (HFM-A), (iii) low-fat meal with reactive hyperaemic stimulus (LFM-R), and (iv) high-fat meal with reactive hyperaemic stimulus (HFM-R). Meals were ingested at 08:00 hours on each treatment day. Brachial artery vasodilation was assessed via ultrasound 4 h after ingestion of each meal. The active hyperaemic stimulus was induced by 5 min of rhythmic handgrip exercise, whereas reactive hyperaemia was induced by 5 min of forearm occlusion. Brachial artery vasodilation was expressed as the percentage change in diameter from baseline to post-active/reactive hyperaemia. Using a  $2 \times 2$  repeated measures ANOVA, a significant stimulus  $\times$  meal interaction ( $P = 0.025$ ) was found. Simple main effects revealed no difference ( $P = 0.541$ ) in brachial artery vasodilation between LFM-A ( $5.75 \pm 1.64\%$ ) and HFM-A ( $6.39 \pm 1.45\%$ ); however, a significant decrease ( $P = 0.014$ ) in brachial artery vasodilation was found in the HFM-R ( $4.29 \pm 1.64\%$ ) compared with the LFM-R ( $7.18 \pm 1.13\%$ ) treatment. In conclusion, the measurement of brachial artery vasodilation in response to active hyperaemia did not detect a change in endothelial function following a single perturbation meal, whereas reactive hyperaemia did.

## INTRODUCTION

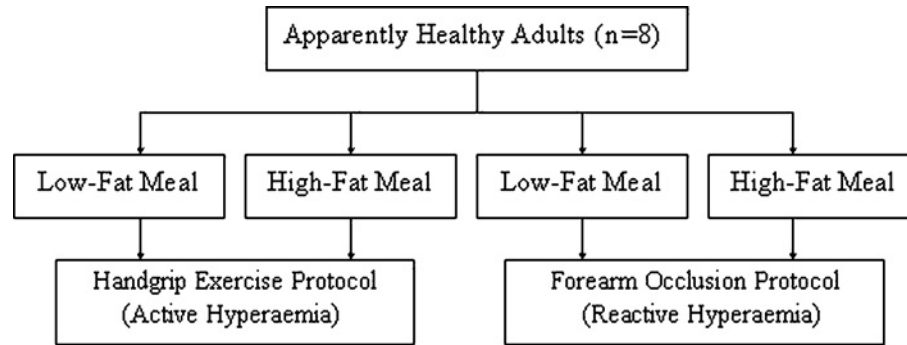
Blood flow exerts a frictional force on the endothelial surface of the vessel lumen known as haemodynamic shear stress [1]. This mechanical stimulus triggers the release of nitric oxide from the endothelium, which is the principal vasodilator [2–5]. Hyperaemia, an increase in blood flow, can be elicited actively and reactively [6]. Active hyperaemia occurs in response to an increase in meta-

bolic activity (i.e. exercise) [7,8], whereas reactive hyperaemia occurs following a transient external occlusion of the vessel [9,10]. In both conditions, hyperaemia generates an increase in shear-stress-induced vasodilation [8,9]. Reactive-hyperaemia-induced brachial artery vasodilation, also referred to as flow-mediated dilation, is used extensively in research to assess changes in endothelial function in a variety of clinical populations and age groups [11–13].

**Key words:** endothelial function, handgrip exercise, hyperaemia, occlusion, shear stress, vasodilation.

**Abbreviations:** IL-6, interleukin-6; TNF- $\alpha$ , tumour necrosis factor  $\alpha$ .

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**Figure 1** Experimental design of the study

Methodological research has focused on establishing optimal protocols to measure endothelial function using the reactive hyperaemic technique [2,3,9,14–16]. Wendelhag et al. [16] and Agewall et al. [2] improved the sensitivity of flow-mediated dilation by having older adults perform a handgrip exercise during occlusion of the artery. Theoretically, the handgrip exercise increased the hyperaemic-induced vasodilation. Rhythmic handgrip exercise alone has also been found to evoke a substantial hyperaemic response that produces vasodilation through a shear stress mechanism similar to the one identified during reactive hyperaemia [17–19]. In a study comparing the vascular function between smokers and non-smokers, Gaenger and co-workers [18] found that smokers, who demonstrated a reduced endothelial function measured via reactive-hyperaemia-induced brachial artery vasodilation, exhibited less of a handgrip-exercise-induced vasodilation of the brachial artery than non-smokers, who had normal endothelial function; however, this difference did not reach statistical significance. In addition, Gaenger et al. [18] reported a significant correlation between exercise-induced vasodilation of the femoral artery and reactive-hyperaemia-induced vasodilation of the brachial artery. Therefore it seems possible that active-hyperaemia-induced vasodilation could be used as an index of endothelial function under physiologically induced shear stress. Whether this method can detect changes in endothelial function, however, has not been examined. Thus the purpose of the present study was to compare brachial artery vasodilation in response to an active compared with a reactive hyperaemic stimulus following a known perturbation of endothelial function. It was hypothesized that active- and reactive-hyperaemia-induced brachial artery vasodilation would respond similarly to the known perturbation.

## MATERIALS AND METHODS

### Experimental design

A within-subjects experimental design (Figure 1) with four treatments, each separated by 2–7 days, was given

to eight apparently healthy adults in a counter-balanced manner. Treatment conditions consisted of: (i) a low-fat meal using an active hyperaemic stimulus, (ii) a high-fat meal using an active hyperaemic stimulus, (iii) a low-fat meal using a reactive hyperaemic stimulus, and (iv) a high-fat meal using a reactive hyperaemic stimulus. Meals were given at 08:00 hours and measurement of brachial artery vasodilation was performed 4 h later. To control for confounding variables, subjects were instructed to fast for 12 h, abstain from exercise for 24 h, abstain from caffeine and tobacco for 12 h, and awake between 06:00 and 07:00 hours, all prior to each treatment [11]. Subjects were asked to remain in the laboratory or minimize physical activity between measurements. All procedures were approved by the Indiana University Committee for the Protection of Human Subjects.

### Subjects

Eight healthy physically active young adults were recruited. None of the subjects had a history of hypertension, diabetes mellitus or tobacco abuse. Exclusion criteria included known gallbladder disease, dietary restrictions to the provided meals, vasoactive medication and brachial artery diameter > 5.0 mm [11]. Written informed consent was obtained from each subject prior to participation in the study.

### Perturbation and control meals

All meals, as used in other studies previously [20,21], were given in the laboratory at 08:00 hours. The low-fat meal comprised of 0 g of fat and 13 mg of cholesterol [3766 J (900 calories)], and the high-fat meal comprised of 50 g of fat, 14 g of saturated fat and 225 mg of cholesterol [3766 J (900 calories)].

### Hyperaemic stimulus

At 4 h after ingestion of the meal, subjects were instructed to lie supine in a dark climate-controlled room (22–24 °C) with their right arm extended out laterally. Each subject underwent an acclimation phase of 20 min to control the haemodynamic response.

### Active hyperaemia

The active hyperaemic stimulus was induced by 5 min of rhythmic (1 s contraction and 1 s relaxation) handgrip exercise, as described previously [19,22]. Briefly, the exercise, performed by the right hand, involved squeezing a hand lever which lifted and lowered a weight (10% maximal voluntary isometric contraction,  $4.0 \pm 0.4$  kg) a distance of 5 cm.

### Reactive hyperaemia

On a separate day, the reactive hyperaemic stimulus was induced by 5 min of right forearm occlusion using a blood pressure cuff inflated to 200 mmHg. After 5 min of occlusion, the pressure was rapidly released to allow for reactive hyperaemia to occur.

### Measurement of brachial artery vasodilation

The brachial artery was imaged longitudinally, 2–10 cm above the antecubital fossa by two-dimensional high-resolution Sonoace Pico ultrasound system (Universal Medical Systems), using a 7 MHz linear transducer. Once a clear artery image was obtained, a still image was captured on the ultrasound (baseline image). Subsequently, the subject underwent either the 5-min handgrip exercise or forearm occlusion condition to elicit the hyperaemic response. The brachial artery was imaged continuously throughout the entire procedure. A still image was captured at 60 s following each 5-min condition. For each still image, five brachial artery diameters were measured in evenly spaced segments approximately every 0.25 cm using B-mode, as described previously [23–25]. The average of five measurements was used to determine the diameter of the artery. Measurements were taken by the same operator, who was blinded to the subject and treatment condition. Brachial artery vasodilation was expressed as the percentage change in diameter from baseline to the post-occlusion diameter value. Reproducibility of our brachial artery diameter measurement has been reported previously [23].

### Blood velocity

Blood velocity (in cm/s) was measured using pulse Doppler at baseline and peak hyperaemia with the Doppler flow signal corrected for an isonation angle of  $70^\circ$ . During the active hyperaemia protocol, subjects were asked to stop contractions for 5 s to minimize arm movement and acquire an accurate active peak hyperaemic velocity half way through the handgrip exercise. The reactive peak hyperaemic velocity was measured within 15 s following the release of the blood pressure cuff.

### Statistical analysis

Descriptive statistics were used to describe the characteristics of the subjects. To test the difference in brachial

**Table 1** Demographic data of the subjects

Values are means  $\pm$  S.E.M. BMI, body mass index; LDL, low-density lipoprotein.

Variable	
<i>n</i>	8
Sex (men/women)	5/3
Age (years)	$25.5 \pm 0.8$
Height (cm)	$170.2 \pm 3.3$
Weight (kg)	$66.4 \pm 3.4$
BMI ( $\text{kg/m}^2$ )	$22.8 \pm 0.6$
Total serum cholesterol (mg/dl)	$169.1 \pm 8.5$
LDL-cholesterol (mg/dl)	$90.6 \pm 4.0$
Maximal voluntary isometric contraction (kg)	$40.4 \pm 4.3$

artery vasodilation and peak hyperaemic velocity between the conditions, a  $2 \times 2$  repeated measures ANOVA (stimulus  $\times$  meal) was performed (SPSS). Simple main effects were evaluated if a significant interaction was found. All data are means  $\pm$  S.E.M. Statistical significance was set at  $P < 0.05$ .

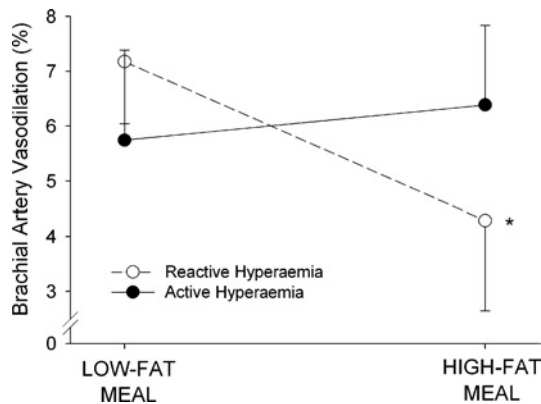
### RESULTS

The demographic information of the subjects is shown in Table 1. Using an independent Student *t* test, within the active and reactive hyperaemic conditions, the order of the meal (low-fat compared with high-fat) did not have an effect on brachial artery vasodilation (active:  $t = 0.623$ ,  $P = 0.556$ ; reactive:  $t = 0.972$ ,  $P = 0.891$ ). Baseline brachial artery diameters, absolute change in diameters and blood velocities are shown in Table 2. Baseline diameters and velocities were similar ( $P > 0.05$ ) among the four treatment conditions. Peak hyperaemic velocities were similar [active:  $F_{(1,14)} = 0.25$ ,  $P = 0.624$ , partial  $\omega^2 = 0$ ; reactive:  $F_{(1,14)} = 0.00$ ,  $P = 0.986$ , partial  $\omega^2 = 0$ ] within the hyperaemic stimulus; however, velocities were significantly lower [ $F_{(1,7)} = 19.68$ ,  $P = 0.003$ , partial  $\omega^2 = 0.368$ ] in active compared with reactive hyperaemia across the two meals. The percentage vasodilation of the brachial artery for each treatment condition is shown in Figure 2. A significant stimulus by meal interaction [ $F_{(1,7)} = 8.09$ ,  $P = 0.025$ , partial  $\omega^2 = 0.181$ ] indicated that the effects of the hyperaemic stimulus (active compared with reactive) were different across the two meals (low-fat compared with high-fat). Simple main effects revealed no difference [ $F_{(1,14)} = 0.39$ ,  $P = 0.541$ , partial  $\omega^2 = 0$ ] in active-hyperaemia-induced vasodilation between measurements following the low-fat and high-fat meals; however, a significant decrease [ $F_{(1,14)} = 7.95$ ,  $P = 0.014$ , partial  $\omega^2 = 0.303$ ] in reactive-hyperaemia-induced vasodilation was found following the high-fat meal ( $4.29 \pm 1.64\%$ ) compared with the low-fat meal ( $7.18 \pm 1.13\%$ ).

**Table 2** Artery diameter and blood velocity values at baseline and during hyperaemia

Values are means  $\pm$  S.E.M. \* $P = 0.015$  compared with the measurement following the low-fat meal during reactive hyperaemia. † $P = 0.002$  compared with the measurement following the low-fat meal during active hyperaemia. ‡ $P = 0.004$  compared with the measurement following the high-fat meal during active hyperaemia.

	Active hyperaemia		Reactive hyperaemia	
	Low-fat meal	High-fat meal	Low-fat meal	High-fat meal
Baseline artery diameter (mm)	3.69 $\pm$ 0.25	3.70 $\pm$ 0.23	3.58 $\pm$ 0.24	3.62 $\pm$ 0.33
Change in artery diameter (mm)	0.21 $\pm$ 0.06	0.23 $\pm$ 0.05	0.24 $\pm$ 0.04	0.14 $\pm$ 0.05*
Baseline blood velocity (cm/s)	11.08 $\pm$ 2.02	8.48 $\pm$ 2.18	11.74 $\pm$ 2.63	8.23 $\pm$ 0.90
Peak hyperaemic blood velocity (cm/s)	47.30 $\pm$ 5.86	50.69 $\pm$ 6.47	88.77 $\pm$ 7.91†	79.58 $\pm$ 5.20‡

**Figure 2** Interaction between active- and reactive-hyperaemia-induced brachial artery vasodilation following a low- and high-fat meal

Values are means  $\pm$  S.E.M. \* $P = 0.014$  compared with the low-fat meal during the reactive hyperaemia stimulus.

## DISCUSSION

The aim of the present study was to compare brachial artery vasodilation in response to an active compared with a reactive hyperaemic stimulus following a known perturbation of endothelial function. The examination of active- and reactive-hyperaemia-induced vasodilation was performed following the ingestion of a low-fat and a high-fat meal. The present study has shown that the measurement of brachial artery vasodilation in response to an active hyperaemic stimulus does not detect a change in endothelial function following a known perturbation meal, whereas reactive hyperaemia does. Even though these results did not support our original hypothesis, these findings are meaningful and suggest that, during active hyperaemia, factors other than shear stress may contribute significantly to the vasodilatory mechanism.

Our perturbation meal (high-fat meal), used previously in other studies [20,21], was used to provoke changes in endothelial function. The high-fat meal has been found to attenuate endothelial function up to 6 h, with peak dysfunction occurring 4 h post-ingestion [20,21,26–28].

In contrast, the low-fat meal has been shown not to influence endothelial function [20,21] and was used as a control condition. We performed the measurement of endothelial function 4 h after ingestion of the meal to coincide with peak endothelial attenuation. The magnitude of change in endothelial function induced by the high-fat meal using reactive hyperaemia was comparable with that reported in the literature [20,21,28]. In addition, the peak reactive hyperaemic velocity and percentage vasodilation observed in our present study are consistent with other investigations utilizing the same forearm occlusion protocol [23,29–31]. The present study utilized the same handgrip exercise protocol and intensity as has been used previously by other researchers [19,22], who aimed to describe the time course of brachial artery diameter and blood flow responses to handgrip exercise. The vasodilation observed in our investigation was comparable with these studies [19,22].

Our present findings are similar to those obtained by Gaenger et al. [18], who found a non-significant difference in active-hyperaemia-induced brachial artery vasodilation between subjects with normal and reduced endothelial function (non-smokers compared with smokers). The non-significant difference in active-hyperaemia-induced vasodilation found in the present study, however, is more notable than that of Gaenger et al. [18], because our experimental design allowed for a comparison using the same group of subjects under different provoked endothelial function status.

The effects of a high-fat meal on endothelial function are well documented in diverse populations [20, 21,26,32,33] and under a variety of assessment techniques [20,34]. The differences found in the present study may be attributed to the hyperaemic technique used. Although the active hyperaemia technique used in the present study has been combined with occlusion in previous reports [2,16], it has not been the sole technique utilized to assess brachial artery vasodilation. Several explanations for the differential effects of the technique can be proposed.

First, differences in peak hyperaemic velocities exhibited by the two techniques may have influenced the outcome. Studies by Wendelhag et al. [16] and Agewall

et al. [2] demonstrated that the addition of handgrip exercise during occlusion of the conduit artery generated a greater vasodilation response than occlusion alone. It has been postulated that the exposure of the endothelium to a greater hyperaemic stimulus improves the sensitivity of the endothelial function measurement, especially in the elderly [2,16]. On the basis of this rationale, the lack of sensitivity of the handgrip exercise in detecting changes in endothelial function found in the present study could be attributed to reduced active hyperaemic velocities. It is possible that the shear stress exerted to the endothelium of the conduit artery during active hyperaemia was not sufficient enough to substantially stimulate the endothelium to generate a response capable of detecting any changes. Although the handgrip exercise utilized in our present study (10% maximal isometric voluntary contraction) appeared somewhat fatiguing to the subject, perhaps a slight increase in intensity would have elicited the required hyperaemic response to detect endothelial changes; however, this hypothesis needs to be tested.

Secondly, the metabolic activity of the muscle may have released substances that influenced smooth muscle relaxation of the conduit artery. We speculate that the existence of these exercise-induced vasoactive substances [i.e. metabolic by-products, ATP and  $P_{O_2}$  (partial pressure of oxygen)] [35], not present during reactive hyperaemia, may have superseded the transient endothelial dysfunction produced by the ingestion of the high-fat meal. Although these substances have an effect on the resistance vessels [35], it is possible for the same response to be reflected in the conduit vessel.

Thirdly, exercise may counteract the oxidative and inflammatory stress associated with the high-fat meal. The underlying mechanisms associated with postprandial endothelial dysfunction are not fully understood [34]. Recently, Tsai et al. [36] proposed that an increase in oxidative stress and depletion of endogenous antioxidants caused by transient hypertriglyceridaemia are responsible for the endothelial dysfunction occurring after ingestion of a high-fat meal. In addition, the increase in oxidative stress generates an inflammatory response reflected by TNF- $\alpha$  (tumour necrosis factor- $\alpha$ ) [37]. On the other hand, skeletal muscle contraction of the quadriceps at 40% of peak power output has been found to release IL-6 (interleukin-6) [38], which has also been found to inhibit TNF- $\alpha$  [39,40]. It could, therefore, be speculated that the production of IL-6 during forearm muscle contraction may have attenuated the endothelial dysfunction associated with the high-fat meal by diminishing the inflammatory response. However, further investigation on the production of IL-6 following local muscle contraction is warranted.

There are a few limitations to the present study. First, the findings of this investigation may not be generalized to older adults or clinical populations. Secondly, although

the use of a single image at 60 s may appear to be a limitation in the present study, we are not the only investigators to utilize a single image [20,28]. Thirdly, the inability to ECG gate and capture simultaneous Doppler blood velocities within our ultrasound system at this time may present another limitation; however, our laboratory has demonstrated the ability to generate valid and reproducible data [23].

In conclusion, the present investigation suggests that the use of active-hyperaemia-induced vasodilation does not detect changes in endothelial function. Further investigations are warranted to determine which factors contribute to the vasodilatory compensation observed during active hyperaemia under a state of transient endothelial dysfunction.

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