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Endothelial Dysfunction Induced by Post-Prandial Lipemia

Complete Protection Afforded by High-Intensity Aerobic Interval Exercise

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Objectives This study was designed to study the effect of exercise and a high-fat meal (HFM) on endothelial function.

Background Post-prandial lipemia and exercise oppose each other in terms of cardiovascular risk; however, the mechanism of their interaction is not well understood.

Methods Endothelial function was assessed by brachial artery flow-mediated dilation (FMD) in 8 healthy men before and after an HFM preceded (16 to 18 h) by rest, a single bout of continuous moderate-intensity exercise (CME), and high-intensity interval exercise (HIIE).

Results Before the HFM, initial brachial artery diameters were similar in all trials (0.43 ± 0.04 cm), but after the HFM, basal diameter decreased only in the control (0.39 ± 0.03 cm) and CME (0.38 ± 0.04 cm) trials. Before the HFM, FMD/shear was improved by a single bout of CME (+20%, $p < 0.01$) and HIIE (+45%, $p < 0.01$; group differences, $p < 0.01$), with no effect in the control trial. After the HFM (30, 120, and 240 min), FMD decayed to a lesser extent with CME, but in a similar fashion to the control trial. In contrast, FMD in the HIIE trial remained elevated following the exercise despite a clear meal-induced lipemia. Although there were no correlations between vascular function and food-induced markers of cardiovascular risk, antioxidant status was strongly correlated with FMD ($r = 0.9$, $p < 0.001$).

Conclusions These findings reveal a clinically relevant protective effect of acute exercise on the vasculature that is clearly exercise intensity dependent and tightly related to exercise-induced antioxidant capacity. (Endothelial Dysfunction Induced by Postprandial Lipemia; NCT00660491) (J Am Coll Cardiol 2009;53:200–6)

Impaired endothelial function is central to the atherosclerotic disease process and serves as a strong independent risk factor for future cardiovascular disease and mortality (1,2). The ingestion of a high-fat meal (HFM) acutely changes the blood lipid profile and reduces endothelial function for many hours after the meal (3). Thus, as a significant proportion of life is spent in the post-prandial state, the factors leading to this transient impairment in endothelial function may well play a key role in the atherosclerotic disease process.

Interestingly, people who perform regular physical activity maintain low lipoprotein levels even after an HFM (4), but this ability is significantly attenuated when a 3-day period of inactivity precedes the HFM. Recently, Gill et al. (3) clearly demonstrated that exercising for 90 min at 50% of maximal oxygen uptake (VO_{2max}) 16 to 18 h before HFM ingestion attenuated the reduction in endothelial function compared with the control situation without exercise. However, this study did not link the changes in endothelial function to either changes in blood lipid profile or a post-prandial inflammatory response and examined only continuous moderate-intensity exercise (CME) at 60% to 70% of maximal heart rate. Thus, the mechanism responsible for this exercise-induced improvement in post-prandial endothelial function, as well as the type of exercise

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that best protects endothelial function in the face of post-prandial lipemia, have yet to be defined.

The coingestion of antioxidant vitamins with an HFM abolishes the post-prandial decrement in endothelial function (5), and it may be that exercise acts through a similar mechanism. Indeed, it is known that exercise training improves the antioxidant status in plasma (6), and, even acutely, there seems to be a mobilization of antioxidants into muscle itself (7). Recently, we reported that high-intensity interval exercise (HIIE) training with intervals at 85% to 95% of maximal heart rate was superior to CME training in terms of improving the cardiovascular risk profile, including endothelial function, and total antioxidant status in plasma, of patients with post-infarction heart failure (6). However, whether this link between oxidative stress, vascular function, and exercise intensity is apparent with a single bout of exercise in healthy subjects, as employed by Gill et al. (3), is currently unknown.

Therefore, this study sought to determine the efficacy of a single bout of 2 different, but clinically relevant, exercise regimens (6) in terms of their ability to attenuate the endothelial dysfunction induced by post-prandial lipemia. It was hypothesized that the 2 very distinct, but isocaloric, exercise sessions of either HIIE or CME would attenuate the post-prandial reduction in endothelial function in an intensity-dependent manner and that this would be related to changes in plasma antioxidant status.

Methods

Subjects. Eight healthy men participated in this study. Exclusion criteria were any known disease, orthopedic and/or neurological limitations to exercise, surgery during the intervention period, drug or alcohol abuse, or participation in another research study. The protocol was approved by the regional ethical committee for medical research, and the study conformed to the Declaration of Helsinki. Written informed consent was obtained from all subjects before inclusion in the study. For each subject, repeated tests were performed at the same time of day.

Study design. Nine days before the first exercise session, VO_{2max} was determined during uphill treadmill running/walking as previously described (6). Each of the 8 volunteers participated in 3 randomized trials (HIIE, CME, and control [no exercise]) with 1 week between each trial, and the starting trial was randomized. The timeline for each trial is shown on the x-axis of Figure 1. Subjects were provided with standardized meals (Fjordland, Norway), which they consumed for 2 days before the 3 trials. Baseline-1 measurements were made in a rested (>48 h) and fasted state (>8 h) before performing the HIIE, CME, or control (resting) trial on the day preceding the HFM. For the 16- to 18-h period after exercise or the control trial, before baseline-2 (fasted state, >8 h) measurements, subjects abstained from exercise, caffeine, and alcohol. Following baseline-2 measurements, subjects ingested the HFM. Endothelial function was then assessed and blood samples taken 30 min, 2 h, and 4 h after finishing the HFM.

Abbreviations and Acronyms

CME = continuous moderate exercise
FMD = flow-mediated dilation
HFM = high-fat meal
HIIE = high-intensity interval exercise
HR_{max} = maximal heart rate
VO_{2max} = maximal oxygen uptake

Exercise. The HIIE was performed on a treadmill and consisted of a 10-min warm-up period at 50% to 60% of maximal heart rate (HR_{max}) followed by 4 intervals of 4 min at an intensity that yielded 85% to 95% of HR_{max}. Between the intervals, the subjects performed 3 min of active recovery at 50% to 60% of HR_{max}. The exercise session concluded with a 5-min cool-down period. To achieve an isocaloric protocol, the CME involved walking continuously for 47 min on the treadmill at 60% to 70% of HR_{max} (8).

HFM. The HFM consisted of a vegetarian mozzarella pizza (Dr. Oetker) with a total weight of 335 g and the following nutritional composition: 48.3 g fat, 80.4 g carbohydrate, 38.5 g protein, and a total of 911.2 kcal. Pilot studies confirmed that in a rested state this meal produced a transient impairment in endothelial function.

Endothelial-dependent vascular function. Endothelial function was assessed by flow-mediated dilation (FMD) of the brachial artery using vascular ultrasound (14 MHz echo Doppler probe, Vivid 7 System, GE Vingmed Ultrasound, Horten, Norway) according to the current guidelines (9). Briefly, measurements were performed on the artery approximately 4.5 cm above the antecubital fossa. After 10 min rest in the supine position in a quiet, air-conditioned room with a stable temperature of 22 ± 1°C, the internal diameter of the brachial artery was assessed. Thereafter, a pneumatic cuff (SC10, Hokanson Inc., Bellevue, Washington) just distal to the elbow on the lower arm was inflated to 250 mm Hg for 5 min and deflated to create an ischemia-induced hyperemia. Blood velocity spectra were recorded 10 s after cuff release to measure peak blood velocity, and thereafter B-mode images were recorded for 5 min to assess artery diameter. To avoid confounding effects of arterial compliance and cyclic changes in arterial dimension, all measurements were obtained at the peak of the R-wave in the electrocardiogram (diastole). The mean of 3 diameter measurements (intima to intima) was recorded using calipers with a 0.1-mm resolution. Shear rate was calculated as blood velocity ($cm \cdot s^{-1}$) divided by vessel diameter (cm) as previously specified (10). All ultrasound images were analyzed in random order using EchoPAC (GE Vingmed Ultrasound AS, Horten, Norway) by an investigator who was blinded to the treatment.

Endothelial-independent vascular function. In an additional set of subjects (n = 8), the complete control protocol (no exercise) was reproduced, but endothelial-independent function was assessed by tracking brachial artery diameter with Doppler ultrasound, as described above, in response to