Is the beneficial effect of prior exercise on postprandial lipaemia partly due to redistribution of blood flow?

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ABSTRACT
Preprandial aerobic exercise lowers postprandial lipaemia (a risk factor for coronary heart disease); however, the mechanisms responsible are still not clear. The present study investigated whether blood flow to skeletal muscle and/or the liver was increased in the postprandial period after exercise, relative to a control trial, and whether this resulted from increased cardiac output or redistribution of flow. Eight overweight inactive males, aged 49.4 ± 10.5 years (mean ± S.D.), acted as their own controls in a counterbalanced design, either walking briskly for 90 min at 60% \( \dot{V}O_2 \text{max} \) (maximal oxygen uptake), or resting in the lab, on the evening of day 1. The following morning, a fasting blood sample was collected, participants consumed a high-fat breakfast, and further venous blood samples were drawn hourly for 6 h. Immediately after blood sampling, Doppler ultrasound was used to measure cardiac output and blood flow through both the femoral artery of one leg and the hepatic portal vein, with the ultrasonographer blinded to trial order. The total postprandial triacylglycerol response was 22% lower after exercise (\( P = 0.001 \)). Blood flow through the femoral artery and the hepatic portal vein was increased by 19% (\( P < 0.001 \)) and 16% (\( P = 0.033 \)), respectively, during the 6-h postprandial period following exercise; however, postprandial cardiac output did not differ between trials (\( P = 0.065 \)). Redistribution of blood flow, to both exercised skeletal muscle and the liver, may therefore play a role in reducing the plasma triacylglycerol response to a high-fat meal on the day after an exercise bout.

INTRODUCTION
It is now more than 30 years since data were published suggesting a mechanistic link between postprandial lipoproteins and atherosclerosis [1]. Case-control investigations have found postprandial TAG (triacylglycerol) concentrations to be positively associated with both CHD (coronary heart disease) [2] and early atherosclerosis [3], and recent epidemiological studies [4,5] suggest that elevated postprandial lipaemia independently predicts risk of developing CHD. Therefore reducing the accumulation of TRLs (TAG-rich lipoproteins) during the postprandial period presents a viable target for lowering arteriosclerotic risk.

Studies in the field of postprandial lipaemia and exercise have consistently shown plasma TAG concentrations to be lowered when moderate-intensity aerobic exercise such as walking is undertaken 11–18 h before an OFTT

Key words: acute exercise, femoral blood flow, hepatic blood flow, oral fat tolerance test, postprandial lipaemia, plasma triacylglycerol.

Abbreviations: 2-D, two-dimensional; A, aortic valve area; AUC, area under the curve; CHD, coronary heart disease; CV, coefficient of variation; eNOS, endothelial NO synthase; HOMA, homoeostasis model assessment; HR, heart rate; iAUC, incremental AUC; LPL, lipoprotein lipase; NEFA, non-esterified ‘free’ fatty acid; OFTT, oral fat tolerance test; RPE, rating of perceived exertion; SV, stroke volume; TAG, triacylglycerol; tAUC, total AUC; VLDL, very-low-density lipoprotein; \( \dot{V}O_2 \), oxygen uptake; \( \dot{V}O_2 \text{max} \), maximal \( \dot{V}O_2 \); VTI, velocity time integral.

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(oral fat tolerance test) [6,7]. Despite the reproducible nature of this lowering, the literature has yet to reach a consensus regarding the mechanism through which such exercise exerts its effect. Early studies suggested that enhanced clearance of TAG, due to increased activity of the enzyme LPL (lipoprotein lipase) within skeletal muscle, was responsible. This belief was largely based on findings from ultra-endurance events, after which substantial increases in postheparin plasma LPL activity were reported [8,9]. However, several investigations have found moderate-intensity exercise to reduce postprandial lipaemia without up-regulation of LPL activity [10–13]; therefore other mechanisms are likely to contribute. Reduced postprandial lipaemia following acute exercise is primarily attributed to a lowering of the plasma VLDL (very-low-density lipoprotein)–TAG concentration [14,15], and indirect evidence, such as an increased serum 3-hydroxybutyrate concentration after exercise [14,15], offers some support for the theory that prior exercise attenuates the postprandial VLDL–TAG secretion rate [16]. However, stable isotope studies in the fasting state do not report a reduction in VLDL–TAG secretion on the morning following exercise [17,18], and investigations of how exercise affects postprandial VLDL kinetics are lacking. Delayed release of dietary fat from the intestine has been proposed to explain at least part of the TAG-lowering effect of exercise [19], but owing to the length of time between cessation of exercise and test meal intake in most studies (typically 12–16 h), it is not likely that any impact on intestinal TAG release would be appreciable enough to significantly influence postprandial lipaemia.

Alongside these suggested mechanisms, it is possible that up-regulation, or redistribution, of blood flow to skeletal muscle and/or the liver may occur on the day following exercise. As the rate of substrate delivery exerts a strong influence upon the extent of substrate uptake from the plasma, increased blood flow to either of these tissues on the day after an exercise bout could potentially reduce plasma TAG concentrations. It has been reported that blood flow to skeletal muscle is maintained above resting levels for at least 90 min after moderate-intensity exercise [20], and earlier work has shown that postprandial, but not fasting, calf blood flow is elevated above control values on the day after a 2-h treadmill run [15]. If blood flow to skeletal muscles used during a treadmill walk is increased on the day after exercise, this increased flow (and assumed greater substrate delivery) would present an opportunity for greater clearance of TAG into the muscle. As the legs contain the major muscles being worked during walking, femoral artery blood flow was monitored in the current study to assess whether blood flow to skeletal muscle exercised on the previous day was increased in the fasting state 13 h later and during a subsequent 6-h postprandial period. Despite the major influence of the liver on lipid metabolism and its theoretical role as the organ largely responsible for the lowering of postprandial lipaemia following moderate exercise, to our knowledge, no published work has investigated whether hepatic blood flow (in the fasted state or postprandially) is altered on the day after an exercise bout. Therefore, in addition to investigating femoral artery blood flow, the present study included measurements of blood flow through the hepatic portal vein. To determine whether any increases in femoral/hepatic blood flow were due to specific redistribution or were secondary to an increase in whole-body blood flow, cardiac output measurements were also made.

### MATERIALS AND METHODS

#### Participants

Eight healthy non-smoking sedentary overweight men gave their written informed consent to participate in the study. Physical characteristics of the participants are presented in Table 1. None of the men performed more than 1 h of structured physical activity per week. All men were free from cardiovascular disease, and none were taking medication known to affect lipid metabolism. All investigative procedures were carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association and ethical approval to conduct the study was granted by the Black Country Research Ethics Committee.

#### Study design

To investigate the effect of brisk walking on postprandial lipaemia and blood flow, volunteers participated in two OFTTs with differing preconditions: a brisk 90-min treadmill walk (EX) and a trial where no prior exercise was performed (CON). The order in which the trials were completed was initially randomized, then counterbalanced, to ensure that an equal number of participants completed the trials in each order. A minimum washout period of 4 days separated OFTTs for each participant. Participants maintained a record of all food and drink consumed on the day prior to and the day of their first trial; this diet was then replicated before the

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**Table 1** Characteristics of the eight study participants

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49.4 ± 10.5</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.72 ± 0.06</td>
</tr>
<tr>
<td>Body mass (kg)</td>
<td>91.7 ± 10.0</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.0 ± 3.0</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>28.8 ± 4.6</td>
</tr>
<tr>
<td>Estimated (V_{0.02}(\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1})) of body weight - min^{-1})</td>
<td>34.3 ± 5.7</td>
</tr>
</tbody>
</table>

Values are means ± S.D. BMI, body mass index.
second trial. No exercise was permitted for 2 days before each OFTT (except that performed during the treadmill walk session), and ingestion of alcohol and caffeine was prohibited on the day prior to the OFTTs.

**Preliminary exercise testing**
To determine the speed and gradient to be used during the 90-min walks, all men participated in a submaximal incremental treadmill test. Participants were advised to select a ‘brisk’ walking speed, but to remember that the speed must be maintainable for 90 min. The speed was guided by HR (heart rate), as recorded using short-range telemetry (Polar Vantage NV, Polar Electro Oy), with values required to be in the 100–110 beats/min range before the speed was deemed sufficient to begin the test. All walking stages lasted for 5 min, with speed held constant and gradient increased by 2–3 % before the start of the new stage. The first stage commenced with a 0 % treadmill gradient. Heart rate was noted and expired gas collected during the final minute of each stage, with indirect calorimetry used to calculate $V_{O_2}$ (oxygen uptake). Upon participants reaching 85 % of their individual predicted maximal HR, i.e. 208–0.7×age [21], the test was concluded. The relationships between HR, oxygen uptake and treadmill gradient were then used to predict $V_{O_2\text{max}}$ (maximal $V_{O_2}$) and the gradient required to evoke 60 % of $V_{O_2\text{max}}$.

**Main trials**

**Exercise trials**
Participants arrived at the laboratory at 18:00 h and completed a 90-min treadmill walk. To confirm that the gradient used was eliciting the desired exercise intensity, 2-min expired breath samples were collected at 15-min intervals during the walk. Subtle alterations to the initial treadmill gradient were made if participants were found to be working above or below their required $V_{O_2}$ values. HR was monitored throughout the trial.

**Control trials**
During control trials, participants underwent a DXA (dual-energy X-ray absorptiometry) scan to determine body fat percentage. Thereafter, participants sat resting in the lab, either watching television or reading, until 90 min had elapsed.

**Evening (post-intervention) meal**
After performing the treadmill walk or resting in the laboratory, all participants were provided with an evening meal. The mean energy ($\pm$S.D.) provided by the meal was 4.39±0.79 MJ (1049±188 kcal) with 36 % of energy as fat, 46 % as carbohydrate and 18 % as protein. The percentage of energy from fat was guided by a U.K. governmental report [22], while the total energy content mirrored each individual’s average evening energy intake as calculated from food and drink diaries maintained by participants for three consecutive evenings prior to their first trial. All participants ingested their evening meal within 60 min of exercise/rest period cessation; participants ate nothing thereafter and drank only water, until the following morning.

**Oral fat tolerance tests**
At 08:00 h on the morning of day 2, participants arrived at the laboratory, and a fasting blood sample (5 ml) was drawn from an antecubital or forearm vein via cannulation (Venflon, Becton Dickinson). Participants remained supine to allow ultrasound measurement of blood flow through the aorta, hepatic portal vein and femoral artery (further details of the methodology employed can be found in the section titled ‘Ultrasound measurements’). The same investigator made all measurements used to derive blood flows and was blinded throughout the study as to whether participants had exercised on the previous evening, thus eliminating any potential bias. A test meal providing 0.91 g of fat, 1.64 g of carbohydrate and 0.41 g of protein/kg of body mass (68.6 kJ/kg of body mass; 50 % fat, 40 % carbohydrate, 10 % protein as percentage of total energy) was then consumed. The meal contained 6.29±0.24 MJ (1504±58 kcal) of energy, had a mean fat load of 83.5±3.2 g and consisted of a raspberry milkshake (whole milk, double cream, sugar and raspberry flavouring), apricot cereal bars, and oven-cooked croissants with butter and raspberry jam.

Venous blood samples were drawn 0.5, 1, 2, 3, 4, 5 and 6 h postprandially. The line was kept patent by flushing every 20 min with non-heparinized saline (B. Braun), and 2 ml of blood was aspirated and discarded at each time-point to clear the cannula before a sample was taken. Immediately after each blood sample, ultrasound measurements were made at the three sites mentioned previously, with participants remaining supine throughout. Participants drank water *ad libitum* during the postprandial period of the first trial; the volume was recorded, and participants were given the same volume of water to consume during the second trial.

**Plasma and serum separation**
At each time-point, a K$_3$-EDTA vacutainer (Becton Dickinson) was precooled on ice to slow metabolism, and 4 ml of blood was transferred from a 5-ml syringe for recovery of plasma. The blood contained within this vacutainer was centrifuged immediately, for 15 min, at 4 °C and 2000 g. Plasma was then aspirated and divided into aliquots for immediate storage at –80 °C. The remaining 1 ml of blood was dispensed into a plain vacutainer for obtainment of serum. This uncoated vacutainer was left on the bench top for 30 min to allow clotting to occur before centrifugation.
Ultrasound measurements

Echocardiographic measurements were made using a Philips Sonos 7500 ultrasound system (Philips Medical Systems) with an S3 2-D (two-dimensional) transducer (1–3 MHz). Digital images of spectral waveforms were recorded for later analysis. For each measurement point, a minimum of three spectral waveforms were recorded at end expiration, or as close as possible to it, before being averaged. By employing this technique, measurements for cardiac output could be averaged in 60-s intervals. HR and a respiratory waveform were also recorded.

An apical five-chamber view of the heart was used with Doppler mode to identify flow through the aortic valve during systole. Using pulsed-wave spectral mode at a screen sweep speed of 100 mm/s, the velocity profile of the aortic flow was obtained. Doppler sampling of the flow was taken immediately below the orifice of the aortic valve. The flow was quantified automatically using the VTI (velocity time integral), which is the mean distance through which blood travels in the outflow tract during ventricular contraction. Each measurement of VTI was made from at least three velocity profiles taken towards the end of expiration. The aortic valve diameter ($d$) was measured from a parasternal long-axis view, thus allowing the aortic valve area ($A$) to be calculated using the formula

$$A = \pi (d/2)^2.$$  

SV (stroke volume) was calculated from VTI $\times A$; cardiac output was calculated from SV multiplied by HR.

2-D and Doppler ultrasound measurements were made using the same ultrasound system (Philips Medical Systems) with a linear-array transducer transmitting a frequency of 12 MHz. Longitudinal images of the femoral artery (proximal to any branching) and the hepatic portal vein were obtained, and the average of several diameter measurements made during the R wave for each vessel was taken. At the same location, blood velocity was measured using pulsed-wave Doppler at the centre of the vessel. Using the 2-D and Doppler ultrasound measurements, blood flow through the femoral artery and the hepatic portal vein was then calculated using the equation

$$V \pi (d/2)^2,$$

where $V$ is the mean velocity of blood flow through the vessel and $d$ is the diameter of the vessel.

As the number of measurements made at each time point for vessel cross-sectional area and velocity of blood flow, for both the hepatic portal vein and the femoral artery, was not equal, it is not possible to report a CV (coefficient of variation) for blood flow through these vessels. Instead, we report the CV for cardiac output and the CVs for the component parts of blood flow for the hepatic portal vein and the femoral artery. CVs were 3.8% for cardiac output, 4.1% for hepatic portal vein cross-sectional area, 5.1% for hepatic portal vein velocity of flow, 2.8% for femoral artery cross-sectional area and 5.5% for femoral artery velocity of flow.

Analytical procedures

Plasma was analysed by enzymatic colorimetric methods using a 96-well plate reader (Multiskan MS, Labsystems) for TAG (Sigma–Aldrich) and using a centrifugal analyser (Cobas Mira Plus, Roche) for NEFAs (non-esterified ‘free’ fatty acids) (Wako) and glucose (ABX Diagnostics). Serum was analysed for insulin by ELISA (IDS Ltd). Owing to the nature of the TAG assay, plasma glycerol concentrations were also measured to allow for correction of TAG concentrations. Samples were stored at $-80^\circ$C until immediately prior to analysis, with all samples for each participant being analysed in the same run. Within-batch CVs were 2.3% for TAG (after correction for plasma glycerol), 1.1% for NEFAs, 2.1% for glucose and 5.7% for insulin.

Calculations and statistics

The total energy expended during the 90-min treadmill walk was calculated using indirect calorimetry, with the assumption of no protein oxidation [23]. The Shapiro–Wilk test was used to test for normality, with none of the data sets found to deviate significantly from a normal distribution. Postprandial metabolites and haemodynamics were analysed using analysis of variance for repeated measures. In addition to the main effects of trial and time, and the interaction between the two, the first two orthogonal polynomial contrasts (linear and quadratic components) were investigated to gain further insight into the shape of the curves over time. These analyses were performed using SYSTAT 11 for Windows. Logarithmic transformation of time (base $e$) was performed prior to statistical analyses for NEFA, glucose, insulin, cardiac output and hepatic portal vein blood flow, as such transformation improved symmetry across time for these variables (a condition for use of orthogonal polynomial contrast analysis). The trapezoidal rule was used to calculate AUC (area under the curve) scores for main measures of interest, thereby allowing comparisons with previous work. $i$AUC (total AUC) responses were calculated using zero as the baseline for the metabolite/blood flow compared time curve, whereas $i$AUC (incremental AUC) responses represent the AUC with baseline reset to the fasting value. In this way, total responses reflect the actual concentration or flow over the study period, whereas incremental responses describe the change in concentration or flow after the meal. $i$AUC scores, $i$AUC scores, fasting values, peak values and time to peak values were analysed using paired sample Student’s $t$ tests (SPSS 16 for Mac). Relationships between variables were examined using Pearson’s product–moment correlation coefficient. Fasting concentrations of glucose and insulin were used to derive a validated surrogate measure of insulin resistance [24]. Specifically, fasting glucose and insulin concentrations were entered into a ‘HOMA2 calculator’ downloaded...
Table 2  Plasma and serum metabolite concentrations, and tissue blood flows, in the fasted state, for both control and exercise trials

<table>
<thead>
<tr>
<th>Measure</th>
<th>Control</th>
<th>Exercise</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma TAG (mmol/l)</td>
<td>1.21 ± 0.14</td>
<td>1.06 ± 0.13</td>
<td>0.062</td>
</tr>
<tr>
<td>Plasma NEFAs (mmol/l)</td>
<td>0.31 ± 0.05</td>
<td>0.33 ± 0.05</td>
<td>0.815</td>
</tr>
<tr>
<td>Plasma glucose (mmol/l)</td>
<td>6.08 ± 0.40</td>
<td>6.27 ± 0.40</td>
<td>0.352</td>
</tr>
<tr>
<td>Serum insulin (pmol/l)</td>
<td>97.8 ± 17.3</td>
<td>111.4 ± 34.3</td>
<td>0.579</td>
</tr>
<tr>
<td>HOMA</td>
<td>1.89 ± 0.34</td>
<td>2.13 ± 0.63</td>
<td>0.583</td>
</tr>
<tr>
<td>Cardiac output (ml/min)</td>
<td>4945 ± 360</td>
<td>5173 ± 298</td>
<td>0.296</td>
</tr>
<tr>
<td>Hepatic portal vein blood flow</td>
<td>174 ± 14</td>
<td>202 ± 21</td>
<td>0.044</td>
</tr>
<tr>
<td>Femoral artery blood flow</td>
<td>372 ± 28</td>
<td>434 ± 51</td>
<td>0.094</td>
</tr>
</tbody>
</table>

from the Diabetes Trials Unit, University of Oxford website (http://www.dtu.ox.ac.uk/index.php?maindoc=/homa/). F ratios were deemed statistically significant when \( P < 0.05 \). Values are presented as means ± S.E.M. unless otherwise stated.

RESULTS

Responses during brisk walking

Participants walked at a speed of 6.0 ± 0.2 km/h up a gradient of 2.9 ± 0.7%. Mean \( V_{O2} \) during the walk was 20.4 ± 1.1 ml · kg\(^{-1}\) · min\(^{-1}\) (59.7 ± 0.6% \( V_{O2max} \)). Gross energy expenditure during the walk was 3.51 ± 0.23 MJ, with a mean HR of 128 ± 3 beats/min. Mean RPE (rating of perceived exertion) from the Borg RPE Scale [26] was 13.1 ± 0.7, i.e. ‘somewhat hard’.

Metabolite concentrations and blood flows in the fasted state

Fasting plasma concentrations of TAG, NEFAs and glucose, serum concentrations of insulin, HOMA (homeostasis model assessment) scores and tissue blood flows are presented (Table 2). Mean plasma TAG concentration tended to be lower after walking, compared with control, but the difference was not statistically significant (see Table 2 for values and significance level). Flows through both the hepatic portal vein and the femoral artery were increased in the fasted state following exercise, relative to control values; however, only the increase in hepatic flow was found to be of statistical significance. When hepatic portal vein blood flow was expressed relative to cardiac output in the fasted state for each trial, the proportion of cardiac output flowing through the hepatic portal vein was not significantly different between trials (mean increase of 10.6% with exercise; \( P = 0.224 \)). The mean percentage of cardiac output flowing through the femoral artery in the fasted state was also unchanged by prior exercise (7.3% increase on control values; \( P = 0.469 \)). Exercise and control trial values for cardiac output, plasma glucose and NEFA concentration, serum insulin concentration and HOMA score were similar, and none of the differences between these variables approached statistical significance.

TAG concentrations in the postprandial state

Plasma TAG concentrations (Figure 1) increased significantly during the postprandial period for both trials (effect of time, \( P < 0.001 \)), but were lower after the walking trial than with control (effect of trial, \( P = 0.002 \)). Prior walking attenuated both the total and the incremental lipaemic response, relative to the control trial (see Table 3 for AUC scores and \( P \) values).

Blood flows in the postprandial state

Cardiac output (Figure 2) was significantly altered across the postprandial period (\( P < 0.001 \) for effect of time); a quadratic function explained 80% of this variation \( (P < 0.001) \). Although cardiac output was increased at all time points on the day after the 90-min walk, relative to control, the difference was modest and did not quite reach statistical significance (effect of trial; \( P = 0.061 \)). A significant change was seen in the flow through the hepatic portal vein (Figure 2) postprandially (\( P < 0.001 \) for effect of time); 79% of this variation could be attributed to a quadratic function \( (P = 0.002) \). Hepatic portal vein blood flow was elevated after exercise, with flow increased at all time points relative to the control trial.

Figure 1  Plasma TAG concentrations in the fasted state (0 h) and for 6 h after intake of a fat-rich mixed meal, following either a 90-min walk (○) or seated rest (●) on the previous evening

Values are means ± S.E.M. The black rectangle represents the point at which the test meal was ingested.
DISCUSSION

The most novel findings within the present study were the observed elevations of hepatic portal vein and femoral artery blood flow on the day after a bout of lipaemia-lowering exercise. The ability of prior exercise to attenuate postprandial TAG concentrations is well known, but to our knowledge, no published work has documented an increase in either fasting or postprandial blood flow to the liver on the day following moderate-intensity exercise. Similarly, while one previous article has reported an increase in calf blood flow, along with a reduction in postprandial lipaemia [14], this finding was on the day after a 2-h run in normal-weight men. We believe ours is the first study to demonstrate an increase in postprandial femoral artery blood flow on the day after a 90-min treadmill walk in a subject group at high risk of developing cardiovascular disease (middle-aged overweight men who possess low cardiorespiratory fitness). When changes in cardiac output were accounted for, only blood flow through the femoral artery remained significantly augmented, signifying a redistribution of blood to the skeletal muscle worked 13–19 h beforehand. The up-regulation of postprandial blood flow through the hepatic portal vein could not be fully explained by the small, non-significant increase in cardiac output seen on the day post-exercise, but equally so, this vessel did not receive a statistically significant redistribution of blood flow. In other words, the significant increase in postprandial portal vein blood flow is partly due to an increase in cardiac output and partly due to receiving a greater percentage of cardiac output.

The observation that blood flow to the liver was increased on the morning after exercise, while the participants were still in the fasted state, was unexpected, and we believe, without precedent. The mean increase in flow was relatively small, but was consistent; all participants displayed an increase with exercise. Although hepatic portal vein blood flow was significantly increased in the fasted state on the morning after exercise, when we believe ours is the first study to demonstrate an increase with exercise. Although hepatic portal vein blood flow was significantly increased in the fasted state on the morning after exercise, when we believe ours is the first study to demonstrate an increase with exercise.

<table>
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<tr>
<th>Measure</th>
<th>Control</th>
<th>Exercise</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma TAG (mmol·l⁻¹·6h⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total response</td>
<td>12.95 ± 1.15</td>
<td>10.16 ± 1.04</td>
<td>0.001</td>
</tr>
<tr>
<td>Incremental response</td>
<td>5.68 ± 0.49</td>
<td>3.77 ± 0.42</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiac output (ml·min⁻¹·6h⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total response</td>
<td>32364 ± 1722</td>
<td>33855 ± 1857</td>
<td>0.065</td>
</tr>
<tr>
<td>Incremental response</td>
<td>2695 ± 1042</td>
<td>2815 ± 568</td>
<td>0.910</td>
</tr>
<tr>
<td>Hepatic portal vein blood flow (ml·min⁻¹·6h⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total response</td>
<td>1301 ± 76</td>
<td>1509 ± 90</td>
<td>0.033</td>
</tr>
<tr>
<td>Incremental response</td>
<td>259 ± 62</td>
<td>296 ± 91</td>
<td>0.648</td>
</tr>
<tr>
<td>Femoral artery blood flow (ml·min⁻¹·6h⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total response</td>
<td>2400 ± 196</td>
<td>2851 ± 167</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Incremental response</td>
<td>170 ± 79</td>
<td>249 ± 163</td>
<td>0.742</td>
</tr>
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The rate of femoral artery blood flow (Figure 2) varied across the postprandial period (P = 0.014 for effect of time), with a quadratic function accounting for 77 % of this variation (P = 0.006). Blood flow through the femoral artery was greater in the exercise trial than the control trial at all time points (effect of trial; P < 0.001). This reflected an increased total response of femoral artery blood flow, but not an increased incremental response (Table 3). The AUC for femoral artery blood flow represented 7.49 ± 0.58 % of cardiac output in the control trial and 8.56 ± 0.59 % in the exercise trial. A significant redistribution of cardiac output to the leg, via the femoral artery (mean increase of 14.4 %), was therefore apparent on the day following exercise (P = 0.010).

Other metabolites in the postprandial state

Concentrations of plasma NEFAs, serum insulin and plasma glucose (Figure 3) changed significantly across the postprandial period (effect of time; P < 0.001 for NEFAs and insulin, P = 0.007 for glucose). NEFA concentrations were higher after exercise than control (P = 0.028), but there was no significant difference between trials for glucose (P = 0.979) or insulin (P = 0.170).
different between trials. This suggests that blood was not selectively redistributed to the liver on the morning after exercise and that differences in cardiac output played a role in the increased portal vein blood flow. However, cardiac output was not significantly greater than control on the morning after exercise, and three of the eight men had a lower cardiac output following the walk.

Therefore the statistically significant exercise-induced increase in hepatic portal vein blood flow in the fasted state appears to be partly due to a small increase in cardiac output and a small redistribution of cardiac output to the liver.
Previous work has shown portal vein flow to be significantly reduced during exercise [27–29], and immediately afterwards [30], although a return to pre-exercise values has been noted as shortly as 10 min post-exercise [28]. The reduction in portal vein flow during cycling exercise at 70% VO2max [29] and after 40 min of treadmill walking/running [30] has primarily been attributed to a reduction in vessel cross-sectional area resulting from splanchnic arterial vasoconstriction. However, reduced portal blood flow after a step test, and recovery of this flow to basal levels, resulted from reduction (and subsequent restoration) of both vessel cross-sectional area and flow velocity [28]. In the present study, the increased fasting portal flow on the day after exercise appears to result from vasodilatation of the vessel, as the diameter of the hepatic portal vein was significantly increased following exercise, but velocity was not significantly altered (results not shown). Speculatively, therefore, the increase in fasting hepatic portal vein blood flow on the day after exercise may result from hyperaemia within the splanchnic arterial vasculature as a reaction to the reduction in flow to the viscera during exercise. Alternatively, a local increase in insulin sensitivity may play a role, as discussed in more detail later.

Hepatic portal vein blood flow increased postprandially in both trials within the present study, with flow still above fasting values at 6 h after meal ingestion. This effect was unsurprising, having been reported previously on more than one occasion [31–35]. Although meal intake has been shown to elevate portal blood flow on several occasions, we believe the significantly greater total flow response following exercise in our study is a new finding. It is not clear exactly how a bout of prior exercise would bring about this change in portal haemodynamics; future studies could address this issue by including measurement of flow within the superior mesenteric artery and in vessels which drain directly into the hepatic portal vein.

Inter-observer variability when measuring portal vein blood flow is large [36–38]; therefore to limit variability as much as possible, the same ultrasonographer made all measurements in the current study. Intra-observer CVs for the component parts of portal vein blood flow, if the same observer is retained [36,37,39], and the CVs for the component parts of portal vein blood flow in our study compare favourably with those found in the literature.

Femoral artery blood flow was not significantly increased in the fasted state on the day after exercise, neither was the incremental flow response significantly elevated, yet the total flow response to the test meal was greater. This apparent contradiction may be explained anecdotally by the observation that most people with increased femoral flow in the fasted state following exercise did not also show a greater response to the meal and vice versa. As a result, all eight subjects demonstrated a larger total femoral artery blood flow response (range: 8.8–35.7% increase in ∆AUC) on the day after exercise than on the day after control. As neither fasting nor 6-h incremental femoral flow was significantly increased, it is difficult to suggest a main mechanism which could explain the finding of enhanced total femoral flow in all subjects; proposition of two possible mechanisms may be more appropriate. First, participants who had elevated fasting femoral blood flow may simply have been seeing the tail end of the massively increased skeletal muscle blood flow from during exercise the previous day. Blood flow to exercising skeletal muscle increases (due to vasodilatation) within seconds of the first muscle contraction [40] and during maximal exercise may increase 20–30-fold above resting values [41]; therefore it is feasible that a modestly elevated flow, of the magnitude seen in the present study (∼1.2-fold increase), may persist in the fasted state some 13 h after cessation of exercise. Although possible, this mechanism does not have strong support, and leg blood flow has been reported to return to pre-exercise values within 2.5 h of completing a 1-h cycle at 60% VO2max [20]. In our present study, femoral artery blood flow was not measured in the period between cessation of exercise and the initial fasting measurements on the morning of day 2; therefore the rate at which leg blood flow returned towards pre-exercise values is not known. If femoral artery blood flow did return to pre-exercise values within 2.5 h of exercise being completed, as in the study of Williams et al. [20], then increases in fasting femoral artery blood flow may instead be explained by a different mechanism: improved insulin sensitivity. A single bout of moderate-to-high intensity exercise can increase whole-body insulin sensitivity, as measured by a euglycaemic–hyperinsulinaemic clamp [42] or a hyperglycaemic–hyperinsulinaemic clamp [43], such that the increase is still detectable 48 h later. Infusion of insulin and maintenance at a high, but physiological concentration has been shown to increase leg blood flow [44]. Therefore, if insulin sensitivity was increased within the skeletal muscles exercised in our study (primarily the legs), then the small concentration of serum insulin present in the fasted state could have increased femoral artery blood flow relative to the control trial. Our own findings showed no correlation between the difference in fasting insulin or HOMA from control to exercise trials, and the difference in femoral artery blood flow, but this does not necessarily discredit the idea that insulin sensitivity may still have been increased at the level of the muscle. In the case of those subjects who did not present with increased femoral blood flow at baseline, but did experience a large increase in flow postprandially in the exercise trial, these individuals may have been more insulin-sensitive during the postprandial period on the day after exercise. In studies showing increases...
in leg blood flow after insulin infusion [44,45], serum insulin is elevated and maintained at a concentration equivalent to or above the peak insulin concentration seen after a mixed meal. However, the elevations in insulin after an oral glucose load [46] and a small mixed meal [47] have also been sufficient to increase skeletal muscle blood flow. Therefore it is perhaps most likely that any exercise-induced improvement in insulin sensitivity would increase femoral artery blood flow most substantially during the postprandial period, when insulin concentrations are high. Exercising aerobically for 60 min at ∼63% \( \dot{V}_O_{2\text{max}} \) was shown to improve postprandial, but not fasting, endothelial function, 17 h later, with the improvement attributed to greater insulin sensitivity after exercise [48]. Prior aerobic exercise may therefore increase skeletal muscle blood flow through improving local insulin sensitivity and ameliorating endothelial dysfunction. Insulin is known to stimulate a distinct phosphorylation-dependent mechanism at the level of the vascular endothelium, ultimately leading to vasodilatation via increased production of NO [49]. Increased sensitivity to insulin action at the site of the vascular endothelium within skeletal muscle could therefore represent a viable mechanism through which femoral artery blood flow is increased on the day after exercise. HOMA scores in the present study were not lower after exercise and therefore do not provide support for this proposed mechanism; however, HOMA only provides an estimation of whole-body insulin sensitivity in the fasted state, it does not offer information regarding the insulin sensitivity of specific tissues, particularly after a meal. Furthermore, HOMA is primarily intended for use as an estimation of insulin sensitivity within a medium to large population; the likelihood of HOMA reflecting insulin sensitivity as measured by clamp, in a very small group of subjects (\( n = 8 \) in the present study), is not high. It may be asked, “what is the mechanism through which prior exercise would produce an insulin-induced increase in blood flow?” Interestingly, postprandial endothelial function (measured by flow-mediated dilatation) was improved by exercise performed 16–18 h earlier [48,50]. Moreover, insulin-sensitive Akt phosphorylation has been shown to be elevated 24 h after a 60-min exercise bout [51]. As there is evidence that NEFAs appear to impair eNOS (endothelial NO synthase) phosphorylation [52,53], the prior exercise might lower the NEFA concentration in the local milieu, thus releasing this inhibition of eNOS.

Although our present results demonstrate that postprandial plasma TAG concentrations are attenuated, and postprandial hepatic portal vein and femoral artery blood flows are increased on the day following a moderate-intensity aerobic exercise bout, relative to a control trial, we can only speculate upon a causative role of the increased tissue blood flows in the lowering of postprandial lipaemia. Speculatively, the elevation of femoral artery blood flow may induce skeletal muscle capillary recruitment (whether ‘longitudinal’ or in previously non-flowing capillaries [54]), thereby increasing skeletal muscle capillary blood volume and presenting an opportunity for more widespread hydrolysis of circulating TAG by LPL within capillaries. However, as evidence from animal studies suggests that capillary blood flow cannot necessarily be determined by extrapolation from flow within larger vessels [55], it therefore does not automatically follow that an increase in femoral artery flow will be reflected at the capillary level. Alternatively, alterations in tissue sensitivity to insulin action, brought about by prior exercise, may act indirectly to reduce postprandial TAG concentrations. Although there was not a statistically significant difference, there was a tendency for postprandial insulin concentrations to be lower after exercise in our present study, when compared with control, despite postprandial glucose concentrations being very similar between trials. Therefore it is possible that postprandial insulin sensitivity was increased with exercise. As skeletal muscle is the primary site of insulin-mediated glucose disposal, it appears reasonable to consider increased postprandial sensitivity to the metabolic actions of insulin on a whole-body level to primarily reflect improved sensitivity within skeletal muscle. Any improvement in skeletal muscle insulin sensitivity is likely to be associated with increased capillary perfusion within the muscle, which would presumably permit circulating TAG greater access to LPL and allow for clearance of such TAG into the muscle, in turn lowering the plasma TAG concentration.

In this scenario, exercise-induced increases in femoral artery blood flow may well be secondary to increases in microvascular blood volume, as capillary recruitment has been shown to precede increases in total muscle blood flow by 60–90 min, as induced by physiological hyperinsulinaemia in rats [56]. Furthermore precapillary arterioles that control microvascular perfusion have been shown to be more sensitive to the vasodilatory effect of insulin than resistance arterioles that control total muscle blood flow [57]. Therefore the increase in femoral artery blood flow in our study may well present a delayed picture of changes that have occurred at the microvascular level and reflect an environment conducive to removal of TAG from the plasma.

Although concerted efforts were made to ensure that the present study was robust, well designed and unbiased, we acknowledge that certain limitations do exist regarding the application and interpretation of our results. First, our observations are limited to measurements made in eight individuals; investigation of a larger group of participants would provide confirmation that the effects we have observed are likely to be truly representative of most middle-aged inactive overweight men. Furthermore, as the eight men in our present study where recruited based on specific criteria, an element of
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Exercise, blood flow and postprandial lipaemia


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