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Acute elevation of lipids does not alter exercise hemodynamics in healthy men: A randomized controlled study

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ABSTRACT

Objective: Exaggerated exercise blood pressure (BP) predicts mortality. Some studies suggest this could be explained by chronic hyperlipidemia, but whether acute hyperlipidemia effects exercise BP has never been tested, and was the aim of this study.
Methods: Intravenous infusion of saline (control) and Intralipid were administered over 60 min in 15 healthy men by double-blind, randomized, cross-over design. Brachial and central BP (including, pulse pressure, augmentation pressure and augmentation index), cardiac output and systemic vascular resistance were recorded at rest and during exercise.
Results: Compared with control, Intralipid caused significant increases in serum triglycerides, very low density lipoproteins and free fatty acids ($p < 0.001$ for all). However, there was no significant difference for any exercise hemodynamic variable ($p > 0.05$ for all).
Conclusion: Acute hyperlipidemia does not significantly change exercise hemodynamics in healthy males. Therefore, the association between raised lipids and increased exercise BP is likely due to the chronic effects of hyperlipidemia.

Q1 1. Introduction

Exercise stress testing is a widely used method to screen for coronary artery disease, and measurement of blood pressure (BP) is a mandatory recording during the test. Some people have an exaggerated rise in BP during exercise testing (e.g. systolic BP > 210 mmHg for men or >190 mmHg for women), and this response has been shown to predict future development of hypertension, irrespective of resting BP values [1]. Moreover, a recent meta-analysis reported that exaggerated BP at moderate intensity exercise (in people free from severe heart disease) predicted cardiovascular events and mortality, independent of resting BP, age, sex and cardiovascular risk factors [2]. The underlying cause of this association is unknown.

Hyperlipidemia is known to increase stiffness of the large central arteries (e.g. carotid, aorta) [3]. During exercise, ejection of increased stroke volume into a non-compliant central vascular system should result in an exaggeration of the normal rise in exercise BP. Indeed, there are reports of both aortic stiffness and hyperlipidemia (total cholesterol-to-high-density cholesterol ratio) being associated with increased brachial BP during maximal exercise [4,5]. We have also shown that regardless of the brachial BP response, central aortic BP (i.e. central systolic BP and/or augmentation index) during moderate intensity exercise is higher when plasma triglycerides [6] or total cholesterol [7] are raised.

Taken altogether, chronic hyperlipidemia is implicated as a possible contributor towards exaggerated exercise brachial and central BP. Whether similar adverse effects can occur in response to acute hyperlipidemia is an important consideration that to our knowledge has never been examined. The aim of this study was to determine the exercise hemodynamic effects of acutely raised serum lipids. In order to limit potential confounding by sex or disease, a middle aged group of healthy men were studied. An intravenous fat emulsion (Intralipid), rather than a fatty meal, was used to raise lipids so that we could study the direct hemodynamic effects without the influence of postprandial metabolism.

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2. Methods

2.1. Participants

Fifteen men (aged 49 ± 8yrs) free from cardiac or metabolic medications were recruited. None had a history of coronary artery disease, diabetes mellitus, left ventricular hypertrophy, aortic valve stenosis, gastric or duodenal ulcers, disease of the liver, pancreas or kidney. The study was approved by the local human research ethics committee and all participants gave written informed consent.

2.2. Study protocol

This was a randomized, double-blind, cross-over study for which resting ventricular–vascular responses have been reported [8]. Participants were examined on two occasions approximately one week apart (each after an overnight fast) at approximately the same time of day. An intravenous cannula was placed in each arm to enable infusion (right) and collection (left) of blood samples. Saline infusion was commenced directly after a baseline blood sample was collected. After 10 min of saline, baseline hemodynamics were recorded. Following this 500U of heparin (in saline solution) was given as a bolus to activate lipoprotein lipase. At the first visit, participants were randomly assigned to receive either saline or Intralipid (20%). At the second visit, the alternate randomization option was prescribed. All infusions were administered at 90 mL/h for 60 min, at the end of which hemodynamic measures were repeated and a blood sample acquired. Immediately after this, whilst infusions were continued, each participant undertook upright seated exercise at a steady state heart rate on a bicycle ergometer. Exercise intensity was set at a fixed resistance of 75 W, as well as at intensities equivalent to 60% and 70% of age-predicted maximal heart rate (220 − age *0.60 or 0.70), and these were performed in step-wise increasing intensity according to the exercise heart rate achieved. Steady state was defined as stable heart rate after at least two minutes exercise at each intensity and, once achieved, all hemodynamic measures (BP, tonometry and echocardiography) were recorded while the participant continued exercising. All measures were acquired within ~90 min of starting infusions and were performed by a person blinded to treatment allocation.

2.3. Hemodynamics

All BP and tonometry measures were recorded in duplicate. An automated BP monitor (52000, Welch-Allyn, NY, USA) was used to measure resting brachial BP, whereas auscultatory mercury sphygmomanometry was used during exercise. Central BP was recorded by radial tonometry using a validated device (SphygmoCor, AtCor Medical, Sydney, Australia) [9]. Radial waveforms were calibrated with the average of the brachial BP measures taken immediately before waveforms. Pulse pressure, augmentation index and pulse pressure amplification were recorded as previously described [7]. Left ventricular volumes were recorded with transthoracic echocardiography using a Vivid 9 ultrasound machine (GE Medical Systems) with a 2.5 MHz transducer. Stroke volume was determined from the difference between end-diastolic and end-systolic volumes recorded from the average of both four-chamber and long-axis views. Cardiac output was defined as; stroke volume × heart rate and systemic vascular resistance as; mean arterial pressure/cardiac output. From our previous exercise reproducibility study [10] it was determined that a between-group difference of 7.6 mmHg in central pulse pressure could be detected during moderate exercise with 15 participants ($\alpha = 0.05$ and $\beta = 0.20$).

2.4. Blood measures

Serum lipids were measured via standard clinical pathology systems (SYNCHRON LX System, Beckman Coulter, CA, USA) and free fatty acids using VITROS 5,1 FS Chemistry System (Ortho-Clinical Diagnostics, NY, USA).

2.5. Statistics

Data were analyzed using SPSS version 18.0 (SPSS Inc, Chicago, Illinois) and presented as mean ± SD with $p < 0.05$ considered significant. Paired samples *t*-tests were used to test for baseline differences between visits as well as the delta values between groups. Pearson correlations were used to determine relationships between variables. Mixed between–within analysis of variance and multivariate statistics were used to determine the main effects for 1) time: as the change of measured variables from rest to each exercise intensity (75 W, 60% and 70% maximal heart rate); 2) intervention: as the comparison for each variable between control and Intralipid and; 3) interaction: as the difference between interventions over time. Analysis was performed at all time points as well as from rest to 75 W only. Significance was determined with the Wilks' Lambda test.

3. Results

There were no significant differences between visits for any baseline variable ($p > 0.05$ for all), nor were there significant differences in workload intensity between groups at 60% (saline 113 ± 42 W, Intralipid 107 ± 38 W) or 70% (saline 152 ± 44 W, Intralipid 150 ± 38 W) age-predicted maximal heart rate (mean difference, 6 ± 14 W and 2 ± 17 W respectively, $p = 0.391$). Baseline serum triglycerides (taken on all participants at saline visit) were significantly correlated with central pulse pressure, augmentation pressure and systolic BP during exercise at 60% maximal heart rate ($r = 0.76$; $r = 0.53$, $r = 0.68$ respectively, $p < 0.05$ for all), but not at rest ($r = 0.42$, 0.28, 0.35 respectively, $p > 0.12$ for all). Low density lipoproteins reduced after Intralipid (3.50 ± 0.78 to 2.81 ± 1.05 mmol/L versus 3.29 ± 0.79 to 3.4 ± 0.82 mmol/L; $p < 0.001$) and there was no change in high density lipoproteins (1.19 ± 0.24 to 1.19 ± 0.24 mmol/L versus 1.15 ± 0.25 to 1.17 ± 0.23 mmol/L; $p = 0.22$) or total cholesterol (5.10 ± 0.74 to 5.07 ± 0.75 mmol/L versus 4.88 ± 0.80 to 4.89 ± 0.86 mmol/L; $p = 0.52$). Compared with control infusion, Intralipid caused significant increases in serum triglycerides (0.86 ± 0.41 to 2.51 ± 1.53 mmol/L versus 1.00 ± 0.57 to 0.68 ± 0.38 mmol/L), very low density lipoproteins (0.39 ± 0.18 to 1.01 ± 0.49 mmol/L versus 0.45 ± 0.25 to 0.31 ± 0.17 mmol/L) and free fatty acids (0.35 ± 0.25 to 1.64 ± 0.55 μmol/L versus 0.33 ± 0.13 to 0.65 ± 0.32 μmol/L) (between-group delta $p < 0.001$ for all). However, there was no significant difference between control and Intralipid infusions for any peripheral or central hemodynamic variable at rest or during exercise (see Table 1; $p > 0.05$ for all, whether assessed at all time points or only from the change from rest to 75 W).

4. Discussion

In this study we have induced an acute increase in serum triglycerides, very low density lipoproteins and free fatty acids, and examined the hemodynamic responses during exercise. This work was undertaken to discern whether the previously reported associations between hyperlipidemia and exaggerated exercise BP (brachial and central) [4,6,7] was a phenomenon related to chronic- or acute-hyperlipidemia. Consistent with previous studies [6,7], highly significant associations were observed between exercise

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Table 1
Hemodynamic variables at rest and during exercise after saline and Intralipid infusion.

Variable	Intervention	Rest	Exercise at 75 W	Exercise at 60% maximal HR	Exercise at 70% maximal HR
Brachial systolic blood pressure (mmHg)	Saline	120 ± 8	140 ± 13	156 ± 17	182 ± 20
	Intralipid	118 ± 10	144 ± 19	156 ± 20	179 ± 19
Central systolic blood pressure (mmHg)	Saline	109 ± 10	117 ± 12	129 ± 14	142 ± 14
	Intralipid	107 ± 11	120 ± 15	126 ± 15	141 ± 14
Central pulse pressure (mmHg)	Saline	32 ± 5	39 ± 5	45 ± 10	55 ± 10
	Intralipid	30 ± 6	40 ± 9	44 ± 9	54 ± 9
Augmentation index (%)	Saline	19 ± 13	8 ± 7	3 ± 10	−6 ± 11
	Intralipid	17 ± 11	6 ± 10	0 ± 10	−4 ± 12
Pulse pressure amplification (ratio)	Saline	1.36 ± 0.17	1.64 ± 0.11	1.73 ± 0.13	1.82 ± 0.08
	Intralipid	1.42 ± 0.18	1.67 ± 0.14	1.76 ± 0.13	1.80 ± 0.10
Mean arterial pressure (mmHg)	Saline	90 ± 10	96 ± 11	105 ± 11	113 ± 11
	Intralipid	89 ± 9	98 ± 12	101 ± 12	111 ± 12
Cardiac output (L/min)	Saline	2.1 ± 1.1	4.5 ± 1.8	4.6 ± 2.1	4.8 ± 1.0
	Intralipid	2.5 ± 0.6	5.2 ± 0.9	5.1 ± 1.9	5.7 ± 1.8
Systemic vascular resistance (PRU)	Saline	34 ± 8	24 ± 10	27 ± 13	24 ± 5
	Intralipid	36 ± 7	19 ± 5	23 ± 10	22 ± 9

central BP and baseline (chronic) lipid concentrations. However, the lack of change in exercise BP (or other hemodynamics) despite significant increases in serum lipids suggests that the underlying vascular causes of exaggerated exercise BP may be related to chronic, rather than acute, exposure to high serum lipids. These observations do not negate the possibility of significant vascular changes occurring in response to acute hyperlipidemia. Indeed, studies have shown impairment of endothelial function with Intralipid and raised free fatty acids [11], possibly occurring via mechanisms involving leukocyte activation from enhanced angiotensin II production in mononuclear and polymorphonuclear cells [12].

Although *a priori* sample size was determined from our exercise reproducibility data [10], the anticipated magnitude of difference between interventions was reasonably large and, as such, subtle hemodynamic effects may have been missed with the relatively small sample. Similarly, greater variability in some methods (i.e. cardiac output measured using echocardiography) may have contributed to the lack of a significant effect from Intralipid. Also there was no significant increase in low density lipoprotein cholesterol after Intralipid infusion and it is possible that acute elevation of this lipoprotein using a different study design would alter exercise hemodynamics. Furthermore, proactive measures to mitigate *ex vivo* inhibition of lipolysis were not carried out and this may have artifactually raised fatty acid concentrations [13]. There also remains the possibility that the exposure time or magnitude of lipid elevation was insufficient to stimulate major hemodynamic responses. Indeed, other studies have reported elevations of resting BP after longer Intralipid infusion periods (1.5–3 h [14] and 4 h [15]), but these studies did not report BP changes over one hour (or exercise BP) and were in patient populations (obese African Americans with type 2 diabetes and patients with Chagas disease) as well as healthy controls. In summary, acute hyperlipidemia, induced by 60 min Intralipid infusion, had no significant impact on exercise hemodynamics in healthy men. These findings suggest that chronic hyperlipidemia has more relevance than acute hyperlipidemia with respect to adverse exercise hemodynamics.

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Disclosure

Dr Sharman has research collaborations with AtCor Medical. None of the other authors declare a conflict.

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