Hypotensive and regional haemodynamic effects of exercise, fasted and after food, in human sympathetic denervation

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1. In human sympathetic denervation due to primary autonomic failure, food and exercise in combination may produce a cumulative blood pressure lowering effect due to simultaneous splanchnic and skeletal muscle dilatation unopposed by corrective cardiovascular reflexes. We studied 12 patients with autonomic failure during and after 9 min of supine exercise, when fasted and after a liquid meal. Standing blood pressure was also measured before and after exercise.

2. When fasted, blood pressure fell during exercise from 162 ± 7/92 ± 4 to 129 ± 9/70 ± 5 mmHg (mean arterial pressure by 22 ± 5%), P < 0.0005. After the meal, blood pressure fell from 159 ± 8/88 ± 6 to 129 ± 6/70 ± 4 mmHg (mean arterial pressure by 22 ± 3%), P < 0.0001, and further during exercise to 123 ± 6/61 ± 3 mmHg (mean arterial pressure by 9 ± 3%), P < 0.01. The stroke distance–heart rate product, an index of cardiac output, did not change after the meal. During exercise, changes in the stroke distance–heart rate product were greater when fasted.

3. Resting forearm and calf vascular resistance were higher when fasted. Calf vascular resistance fell further after exercise when fasted. Resting superior mesenteric artery vascular resistance was lower when fed; 0.19 ± 0.02 compared with 0.32 ± 0.06, P < 0.05. After exercise, superior mesenteric artery vascular resistance had risen by 82%, to 0.53 ± 0.12, P < 0.05 (fasted) and by 47%, to 0.29 ± 0.05, P < 0.05 (fed).

4. On standing, absolute levels of blood pressure were higher when fasted [83 ± 7/52 ± 7 compared with 71 ± 2/41 ± 3 (fed), each P < 0.05]. Subjects were more symptomatic on standing post-exercise when fed.

5. In human sympathetic denervation, exercise in the fed state lowered blood pressure further than when fasted and worsened symptoms of postural hypotension.

INTRODUCTION

Food and exercise independently lower blood pressure (BP) in subjects with sympathetic denervation due to primary autonomic failure (AF), even in the supine position [1–4]. In such subjects food lowers BP due to vasodilatation in the splanchnic circulation unopposed by peripheral vasoconstriction or an increase in cardiac output [5, 6]. In AF, exercise reduces BP as a result of vasodilatation in exercising skeletal muscle and inadequate splanchnic vasoconstriction [7]. In clinical practice, food ingestion can enhance the symptoms of postural hypotension in AF [8]; a similar effect occurs after exercise [9]. To determine if the combined effects of food and exercise had a cumulative blood pressure-lowering effect on supine BP and standing BP post-exercise in subjects with AF, we studied the systemic and regional haemodynamic effects of exercise when fasted with those of exercise after a liquid meal.

SUBJECTS

Twelve subjects (mean age 56 years, 5 male, mean weight 78 kg, range 52–82 kg) with chronic primary autonomic failure were studied. Eight had pure autonomic failure with no other neurological deficits, and four had multiple system atrophy (the Shy-Drager syndrome) with accompanying extra-pyramidal, cerebellar and/or pyramidal features. The diagnosis was confirmed by a series of physiological and biochemical (plasma noradrenaline) responses to autonomic function tests [10, 11]. Both groups had abnormal responses to the Valsalva manoeuvre and pressor tests (mental arithmetic, cutaneous cold and isometric exercise). In both groups, sinus arrhythmia was reduced and there was an abnormal

Key words: blood pressure, exercise, food, sympathetic denervation.

Abbreviations: AF, autonomic failure; BP, blood pressure; CPR, calf peripheral resistance; CVR, calf vascular resistance; FVR, forearm vascular resistance; HR, heart rate; MAP, mean arterial pressure; SD, stroke distance; SDH, stroke distance–heart rate product.

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sudomotor response to a 1°C temperature rise. None had evidence of secondary autonomic failure, as is associated, for example, with diabetes mellitus. All had symptomatic postural hypotension (a fall of more than 30 mmHg systolic pressure when upright) with symptoms such as dizziness, visual disturbances and fainting, suggestive of cerebral ischaemia during postural change. The findings were consistent with severe sympathetic denervation. All medication, except fludrocortisone, was stopped at least 72 h before the study. The six subjects who were on regular treatment with low-dose fludrocortisone (maximum of 200 μg daily) took the last dose 12 h before exercise. The study was performed with the understanding and consent of each subject and was approved by the Ethics Committees of the National Hospital for Neurology and Neurosurgery and St. Mary's Hospital.

PROTOCOL

All subjects performed two identical exercise studies on two separate occasions, commencing at 09.00 h in a temperature-controlled clinical laboratory (average temperature 24 ± 2°C). The first study was performed after an overnight fast with water only, the second 30 min after a liquid meal of Complan with glucose in a milk base (66 g of carbohydrate, 30 g of protein and 15 g of fat, 2300 kJ). After 30 min of supine rest, the subjects exercised for 9 min in the supine position by continuously pedalling a cycle ergometer at workloads of 25, 50 and then 75 W, each for 3 min. Measurements were made during exercise at the end of each stage and continued for 10 min post-exercise. To assess the effects on postural hypotension, BP measurements were also made after 2 and 5 min of standing pre-and post-exercise. The length and severity of the exercise protocol was chosen on the basis of results from previous studies in subjects with primary autonomic failure [2], in whom this protocol was found to be the maximum level of exercise that the majority could perform while on no treatment.

METHODS

BP and heart rate (HR) were recorded with an automated sphygmomanometer (Sentron, Bard Biomedical, U.S.A.) which was calibrated against a mercury sphygmomanometer. Automated sphygmomanometry measurements of BP during exercise correlate well with those using Finapres during a protocol in subjects with AF and normal subjects identical to the one used in this study [12]. Resting values pre-exercise were calculated from the mean of three readings over 5 min; all other readings represent one BP measurement. Mean arterial pressure (MAP) was calculated as the diastolic pressure plus one-third of the pulse pressure. Stroke distance (SD) was derived from the integral of peak velocity profile of ascending aortic blood flow, measured by continuous wave Doppler ultrasound (Exerdop; Quinton Instrument Company, Parkway, Bothell, WA, U.S.A.). The transducer was placed in the suprasternal notch with adequate coupling fluid and positioned to aim the beam towards the anticipated location of the aortic root. The major source of error in Doppler measurements of stroke distance is underestimation of aortic velocity because the transducer has not been aimed to produce the optimum Doppler angle. Care was taken to ensure the highest systolic velocity integrals were obtained. These were associated with characteristic high-pitched, crisp, clear sounds during systole with a rapid onset, falling to a minimum during cessation of flow in diastole. The maximum Doppler frequency shift in the signal corresponding to the maximum velocity of the blood from the ascending aorta, occurring at any moment, was recorded during 20 complete and consecutive cardiac cycles and stroke distance was calculated from continuous integration of each systolic velocity integral. The stroke distance–heart rate product (SDH), a measure of relative cardiac output, was calculated by multiplying SD by HR. This method has been validated and SDH considered a measure of cardiac output at rest [13] and during exercise [14], and has been used previously during supine exercise [15] and in subjects with sympathetic failure [16]. Changes in SDH using this method are reproducible (c.v. 9% compared with 8.5% for thermodilution [13]). A mean value of 20 consecutive and complete cardiac cycles was taken for each observation. Results are presented as the percentage change in SD and SDH from resting levels. Calculated peripheral resistance (CPR) was determined by dividing MAP by SDH. Forearm and calf muscle blood flow were calculated from strain-gauge plethysmography during venous occlusion, using a cuff placed around the forearm or above the knee, from plethysmographic slopes using a previously described formula [17]. Strain gauges were applied at the widest portions of the forearm and upper calf. To ensure that blood flow measurements excluded contribution from the hand and foot circulations, cuffs were placed at the wrist and ankle and inflated to 50 mmHg above systolic arterial pressure, 1 min before flow measurement.

Superior mesenteric artery blood flow was measured using real-time, pulsed Doppler flowmetry (Acuson 128 Computed Sonography System, Acuson Corporation, CA, USA; 3.5 MHz sector transducer), using methods described previously in our unit in subjects with autonomic failure [16, 18]. Superior mesenteric artery vascular resistance, forearm vascular resistance (FVR) and calf vascular resistance (CVR) were calculated by dividing MAP by the flow. All these techniques have been validated and described previously [13, 16, 17].

Statistics

Results are expressed as means ± SEM, except for superior mesenteric artery, forearm and calf blood
flow, which were not normally distributed and therefore have been expressed as medians and interquartile ranges. Percentage changes were calculated as mean percentage changes for both normally and non-normally distributed data. Paired t-tests were used to analyse changes from baseline in fasted and fed states, and a factorial analysis of variance for repeated measures was used to compare changes when fasted and when fed. T-tests with Bonferroni correction were used to compare changes at each time point. Non-parametric data were analysed using Mann–Whitney U-tests to compare changes between fasted and fed states and Wilcoxon signed rank tests to analyse changes from baseline in fasted and fed states for superior mesenteric artery, forearm and calf blood flow data.

In each of the Figures the horizontal axis denotes notional time, as time is not represented on a linear scale.

RESULTS

Blood pressure

Resting supine BP was higher pre-exercise when fasted (162±7/92±4) as the meal reduced resting BP in the fed state from 159±8/88±6 to 129±6/70±4 mmHg (MAP by 22±3%, \(P<0.0001\) fasted compared with fed) (Table 1). The pattern of MAP response was significantly different in fasted and fed states (\(P<0.05\); during exercise, when fasted, MAP fell from 116±5 to 90±6 mmHg (22±5%), \(P<0.0005\) (Fig. 1). When fed, MAP fell from 90±4 to 82±4 mmHg (9±3%), \(P<0.01\), after 9 min exercise (Fig. 1). In the fasted state, MAP was significantly higher than when fed, at rest, after 3 and 6 min of exercise and at 2 and 5 min post-exercise (Fig. 1).

Heart rate

Resting supine HR was lower when fasted (69±2 beats/min) than when fed (79±3 beats/min), \(P<0.0001\), as HR rose after the meal from 70±3 to 79±3 beats/min, \(P<0.0001\). The pattern of HR response was significantly different in fasted and fed states (\(P<0.05\)); HR rose further during exercise when fasted (42±5% compared with 25±3%, \(P<0.0003\)). However, at the end of 9 min exercise, HR was not significantly different in fasted and fed states (Table 1).

Stroke distance, stroke distance–heart rate product, calculated peripheral resistance

Absolute measurements of stroke volume and cardiac output depend on aortic diameter which was not measured; therefore, resting values of SD and SDH when fasted and fed have not been compared.

The pattern of response was not significantly different in the fasted and fed states, although SD increased maximally when fasted only after 3 min of exercise, by 19% (\(P<0.05\)), and there were no changes during exercise when fed (Fig. 2).

Resting SDH did not change significantly after the meal and the pattern of response was not significantly different in the fasted and fed states (Table 1). Changes in SDH were greater, although not significantly, at all stages of exercise when fasted; at 3 min, 52±15% versus 24±10%; at 6 min, 42±10% versus 20±10%; at 9 min, 45±13% versus 35±10% (Fig. 3).

At rest, CPR was higher when fasted than when fed, \(P<0.0001\) (Table 1), and the pattern of response was significantly different in the two states (Fig. 4). During exercise, CPR decreased more when fasted.

Superior mesenteric artery blood flow and vascular resistance

Readings of superior mesenteric artery blood flow were not obtained during exercise in the fed state, due to difficulty in visualizing the superior mesenteric artery, probably as a result of bowel gas; we

| Table 1. Systolic and diastolic blood pressure (SBP and DBP), heart rate (HR), stroke distance–heart rate product (SDH) and calculated peripheral resistance (CPR) during the last stages of exercise and 5 and 10 min post-exercise when fasted and fed. Results are means(SEM). Significance of changes from baseline: *\(P<0.05\), **\(P<0.005\), ***\(P<0.0001\); significance of differences between fasted and fed states, \(tP<0.05\), \(ttP<0.01\), \(tttP<0.0005\). |
| --- | --- | --- | --- |
| SBP (mmHg) | Resting | Exercise 9 min | Post-exercise 5 min | Post-exercise 10 min |
| Fasted | 162±5/92±4 | 129±3/86±4 | 133±3/88±4 | 137±3/91±4 |
| DBP (mmHg) | Resting | Exercise 9 min | Post-exercise 5 min | Post-exercise 10 min |
| HR (beats/min) | Resting | Exercise 9 min | Post-exercise 5 min | Post-exercise 10 min |
| Fasted | 69±1/42±1 | 56±1/39±1 | 69±1/44±1 | 78±1/51±1 |
| Fed | 70±1/50±1 | 66±1/49±1 | 72±1/53±1 | 72±1/53±1 |
| SDH (units) | Resting | Exercise 9 min | Post-exercise 5 min | Post-exercise 10 min |
| Fasted | 736±90±9 | 1043±90±9 | 900±90±9 | 875±90±9 |
| Fed | 923±90±9 | 1216±90±9 | 925±90±9 | 881±90±9 |
| CPR (units) | Resting | Exercise 9 min | Post-exercise 5 min | Post-exercise 10 min |
| Fasted | 0.16±0.01 | 0.09±0.01 | 0.12±0.01 | 0.12±0.01 |
| Fed | 0.09±0.01 | 0.07±0.01 | 0.09±0.01 | 0.11±0.01 |
therefore compared resting measurements when fasted and fed with those taken after exercise ceased. In previous studies in AF in our laboratory where measurements of superior mesenteric artery blood flow were obtained during exercise, readings at 2 min post-exercise were not significantly different from those made in the final stages of exercise [7] and thus may be taken as a measure of changes occurring during exercise in these subjects.

Resting superior mesenteric artery blood flow was not significantly lower when fasted, 351 (287–683) versus 452 (296–658) ml/min. Resting superior mesenteric artery vascular resistance was higher when fasted (0.32±0.06 versus 0.19±0.02 units, \( P<0.02 \)). At 2 min post-exercise, superior mesenteric artery blood flow fell when fasted and fed: when fasted, to 193 (165–370) ml/min, \( P<0.03 \) and when fed, to 317 (206–411) ml/min, \( P<0.01 \) (Table 2).

When fasted superior mesenteric artery vascular resistance rose, to 0.53±0.12 units, \( P<0.05 \), 2 min post-exercise and when fed, to 0.29±0.05 units, \( P<0.05 \) (Table 2).

**Forearm and calf blood flow and vascular resistance**

Resting supine forearm blood flow was similar when fasted and fed, 3.0 (2.1–3.7) and 3.7 (2.7–4.6) ml min\(^{-1}\) 100 g\(^{-1}\) respectively. Resting FVR was higher when fasted \( (P<0.01) \); FVR fell after the meal \( (P<0.05) \). There were no changes in forearm blood flow after exercise when fasted or fed and no further changes in FVR when fed (Table 2); however, when fasted, FVR fell at 5 min post-exercise \( (P<0.05) \). Resting calf muscle blood flow was similar when fasted and fed, 2.8 (1.8–3.6) and 3.4 (2.5–3.8) ml min\(^{-1}\) 100 g\(^{-1}\) respectively (not significant); however, resting CVR was higher when fasted (46±8 versus 32±4 units, \( P<0.05 \)), as CVR fell after the meal from 43±6 to 32±4 units, \( P<0.05 \). There were no changes in calf muscle blood flow after exercise when fasted or fed (Table 2). When fasted, CVR did not fall significantly; there were no further changes in CVR after exercise in the fed state.

**Blood pressure responses to standing**

At 10 min post-exercise, the majority of subjects were unable to stand for 5 min; therefore data at 2 min of standing only has been presented. After
exercise, although the change in BP on standing was similar for fasted and fed states (54 ± 7/25 ± 4 mmHg and 50 ± 4/30 ± 4 mmHg respectively), the absolute level of BP when standing was higher when fasted (83 ± 7/52 ± 7 mmHg compared with 71 ± 2/41 ± 3 mmHg, each \( P < 0.05 \)). Cerebral perfusion probably depends more on the absolute level of BP than the change as all subjects were more symptomatic on standing after exercise when fed.

**DISCUSSION**

In this study in AF, BP fell to lower absolute levels during exercise when fed. BP was substantially reduced after the meal, so resting BP was lower in the fed state even before exercise began. This was because of a reduction in resting CPR due to dilatation in the splanchnic and skeletal muscle vascular beds. The splanchnic vasodilator effects of food have been well documented [19, 20]. Reduction in FVR and CVR after the meal indicated active vasodilatation in skeletal muscle but the mechanism of this effect was uncertain. Previous studies of meal ingestion in subjects with AF have reported no change in skeletal muscle vascular resistance [4, 21]; however, a significant reduction in leg vascular resistance has been reported after 75 g of glucose in subjects with AF [22]. The reduction in skeletal muscle vascular resistance after the meal in our study may reflect the skeletal muscle vasodilatory effects of insulin [23]; similar changes in forearm vascular resistance to those in our study have been described using strain-gauge plethysmography after insulin infusion to physiological levels in normal subjects [24]. Dilatation in other vascular beds, such as the renal vasculature, may also have contributed to the reduction in CPR after the meal, since food increases renal blood flow [25].

In the present study, SDH did not change after food, indicating lack of cardiac compensation, which in the presence of reduced CPR also would have contributed to low resting BP, in agreement with previous studies of food ingestion in subjects with AF [4].

During exercise when fed, the fall in BP from lowered resting values appeared to be due to a further reduction in CPR. Superimposition of skeletal muscle vasodilatation on an already reduced CPR should arguably have resulted in even lower BP than that observed. Although CVR had not fallen after

![Graphs](image-url)
exercise when fasted or fed, since measurements of calf blood flow could not be made during exercise and measurements were not made in the upper leg, we cannot discount dilatation in exercising skeletal muscle contributing to the fall in CPR. In the fed state, a further explanation for the lack of change in CVR is that maximal dilatation in skeletal muscle may have already occurred after the meal, explaining why there was no further reduction in CVR and less of a BP fall than expected. The reason for the fall in FVR after exercise when fasted is unclear. In the absence of sympathetic vasoconstrictor action, the observation may represent the unmasking of vasodilatory effects of circulating metabolic substances, to which AF may be particularly sensitive.

During exercise, superior mesenteric artery vascular resistance rose less when fed, suggesting that impaired splanchnic responses contributed to BP reaching lower levels than when fasted. Subjects with AF are able to increase superior mesenteric artery vascular resistance during exercise, although changes follow a slower time course compared with normal subjects [7], raising the possibility that a gradually released or slowly converted vasoconstrictor substance is involved. Neither food ingestion [4] nor exercise [2] raise plasma adrenaline levels in such subjects with sympathetic denervation; the effects of adrenal medullary stimulation are therefore unlikely to have contributed to the systemic or regional haemodynamic responses after food ingestion or exercise in this study. Although changes in angiotensin receptor function may occur as a result of fludrocortisone therapy [26], this is also unlikely to have contributed, since the responses were no different in the subjects treated with fludrocortisone.

Less superior mesenteric artery vasoconstriction during exercise in the fed state may have occurred because of the vasodilatory effects of hormones released after food ingestion, such as vasoactive intestinal polypeptide, neuretin and Substance P [27]. Vasoconstrictor substances are released during exercise in AF [28] but in the fed state these may not have had the same effect on the splanchnic vasculature as they did when fasted; the main site of the increase in blood flow after meal ingestion is the mucosal circulation [29, 30] which also displays a greater capacity than other parts of the intestinal circulation to ‘escape’ from vasoconstriction [31].

There were differences in HR response to exercise when fasted and fed. Increases in HR in AF after food ingestion may be mediated by vagal withdrawal [6] and may be the mechanism for the rise in HR during exercise in AF. Near-maximal vagal inhibition after food might explain the smaller change in HR during exercise in the fed state. The overall SD responses were not significantly different in the fasted and fed states; SD does not increase during exercise in normal subjects [2].

In the fasted state in AF the rise in cardiac output during exercise is similar to that in normal subjects [2]. SDH responses in our study were not significantly different in the fasted and fed states, suggesting that differences in cardiac output are unlikely to explain the differences in BP in the two states. Our results contrast with studies in normal subjects after food ingestion, in whom increments in cardiac output during exercise are greater in the fed state during 2 min bouts of moderate, rhythmic exercise [32] and splanchnic blood flow appears to be maintained [32, 33]; this demonstrates the ability of the intact autonomic nervous system to increase cardiac output to supply exercising muscles.

In AF, postural hypotension is the result of venous pooling, especially in the lower limbs, accompanied by inadequate compensatory vasoconstriction in skeletal muscle and the splanchnic vascular bed [16]. Further vasodilatation, in skeletal muscle after exercise and in the splanchnic bed after food, probably caused BP to fall to even lower levels.
on standing after exercise when fasted and fed. However, although the fall in BP on standing was similar in the fasted and fed states, the absolute levels of BP on standing were lower after exercise in the fed state and subjects were more symptomatic. This indicates, as previously noted [28, 34], that absolute levels of BP, rather than changes, are of critical relevance in determining cerebral perfusion and the symptoms of cerebral ischaemia.

In summary, in subjects with AF who were fasted, a reduction in CPR contributed to hypotension during exercise; in the fed state the fall in CPR occurred mainly after the meal without much further fall during exercise. The prime mechanism for the lack of a greater hypotensive effect of exercise when fed is unclear; the calf muscle vessels may have been maximally vasodilated after the meal, before exercise, or a circulating vasoconstrictor may have prevented further reduction in CPR. From the clinical standpoint, subjects were more symptomatic on standing after exercise when fed. We conclude that in AF, the combination of food and exercise caused BP to fall to lower levels and was associated with greater symptoms of postural hypotension.

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REFERENCES