Effect of the somatostatin analogue, octreotide, on exercise-induced hypotension in human subjects with chronic sympathetic failure

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1. In autonomic failure, supine exercise lowers blood pressure and worsens postural hypotension. The somatostatin analogue, octreotide, reduces postprandial and postural hypotension, but its effects on exercise-induced hypotension and on postural hypotension post-exercise are unknown.

2. Eighteen subjects with chronic sympathetic denervation were studied; 12 had pure autonomic failure and six had additional neurological features of the Shy–Drager syndrome. Haemodynamic, hormonal and biochemical changes were measured before, during and after incremental supine leg exercise on two occasions: on no treatment and after subcutaneous octreotide. Exercise was performed 120 min after octreotide in eight subjects and 60 min after octreotide in ten subjects.

3. Octreotide did not improve exercise-induced hypotension; the blood pressure fall was greater during exercise, but the blood pressure level was no different than without treatment. Heart rate, stroke distance, cardiac index and systemic vascular resistance were similar at rest and changed to the same degree with exercise on and off octreotide. After octreotide, resting levels of serum growth hormone, plasma noradrenaline, adrenaline and renin were unchanged, but glucose was higher and insulin was lower. There was no change in biochemical and hormone levels during exercise either off or on octreotide.

4. After octreotide, although the rate of blood pressure recovery was similar post-exercise, the levels of blood pressure were higher than in the non-treatment phase and postural hypotension was improved before and after exercise.

5. In conclusion, in primary autonomic failure, octreotide did not improve exercise-induced hypotension in the supine position, suggesting that octreotide-sensitive vasodilatory peptides do not contribute to the blood pressure fall. With octreotide, supine blood pressure levels were higher post-exercise and postural hypotension was improved both before and after exercise.

INTRODUCTION

The majority of subjects with chronic autonomic failure (AF) notice an exacerbation of their postural hypotension symptoms during or after even mild exertion. Physiological studies in such subjects indicate that exercise lowers blood pressure (BP) even in the supine position [1-3] and worsens postural hypotension post-exercise [4]. Although the haemodynamic mechanisms accounting for this are partly known, the role of vasodilatory substances, including peptides such as insulin, is unclear. The somatostatin analogue octreotide, which inhibits release of a range of peptides, is of benefit in the management of post-prandial hypotension [5], and reduces postural hypotension both before and after eating [6]. It also improves walking time [7]; this may be due to a reduction in exercise-induced hypotension. We therefore studied the cardiovascular and hormonal effects of octreotide during and after supine exercise in subjects with primary AF. The effects of octreotide on postural hypotension pre- and post-exercise were also studied.

METHODS

Subjects

Eighteen subjects with primary chronic AF were studied, of which 12 were male and six female, with a mean age of 61 years (range 40–78 years). Twelve had pure AF with no other neurological deficits and six had accompanying extrapyramidal, cerebellar and/or pyramidal features consistent with a diagnosis of Shy–Drager syndrome (often used synonymously with multiple system atrophy).
All had symptomatic postural hypotension [systolic blood pressure (SBP) fall of more than 30 mmHg], with symptoms such as dizziness, visual disturbances and fainting indicative of cerebral ischaemia during postural change. All had sympathetic vasoconstrictor failure on physiological testing [8], with an impaired plasma noradrenaline response to head-up tilt. The majority of subjects also showed evidence of cardiac parasympathetic impairment on testing. Secondary causes of AF, such as diabetes mellitus, were excluded. All medication, except fludrocortisone, was stopped at least 72 h before the study. The 16 subjects who were on regular treatment with low-dose fludrocortisone (maximum 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 committee of the National Hospital for Neurology and Neurosurgery.

Protocol

All subjects performed two identical exercise studies on separate occasions, commencing at 09.00 hours in a temperature-controlled clinical laboratory (average temperature 24 ± 2°C), after an overnight fast with water only. The studies were either performed after administration of 1 μg/kg octreotide subcutaneously or on no medication, in a random order which was neither patient nor observer blind. None of the subjects could voluntarily raise their BP, as indicated by a lack of pressor response to a range of tests (mental arithmetic, isometric exercise and cutaneous cold) during autonomic testing. It was therefore not considered justified to subject them to placebo injections. In the first eight subjects (group 1), octreotide was given 120 min before exercise. After studying these results, with no improvement in exercise-induced hypotension, a further ten subjects (group 2) were exercised 60 min after octreotide to maximize drug effect.

After a 30 min supine rest, the degree of postural hypotension was measured after 2 and 5 min of standing. After a further 30 min rest, the subjects exercised for 9 min in the supine position by pedalling a cycle ergometer at workloads of 25, 50 and then 75 W, each for 3 min. Measurements were made at the end of each stage of exercise and continued for a further 10 min post-exercise. The degree of postural hypotension was then reassessed post-exercise. The length and severity of the exercise protocol was chosen as this was known, from a study of subjects with primary autonomic failure [3], to be the maximum level of exercise that the majority could perform while on no treatment. No other measure of workload (such as oxygen consumption) was made as each subject performed an identical exercise protocol with and without treatment.

Measurements

SBP and diastolic blood pressure (DBP) and heart rate were recorded with an automated sphygmomanometer (Dinamap, Critikon, Tampa, FL, U.S.A.), which was calibrated against a mercury sphygmomanometer. Resting values pre-exercise were calculated from the mean of three readings over 5 min; all others were from one reading. Mean arterial blood pressure was calculated as DBP plus one-third of the pulse pressure. In the second group of subjects, cardiac index, as a measure of relative cardiac output, was calculated by multiplying stroke distance by heart rate. Stroke distance was derived from the integral of peak velocity profile of ascending aortic blood flow, measured by a continuous wave Doppler ultrasound technique (ExerDop; Quinton Instrument company, Seattle, WA, U.S.A.). A mean velocity of 20 consecutive cardiac cycles was taken for each observation. This technique has been validated as a measure of cardiac output at rest [9] and with exercise [10], and has been used previously with supine exercise [11, 12].

An index of systemic vascular resistance was calculated from mean arterial pressure/cardiac index. In the second group of subjects, skin temperature was measured using thermistor probes (Panlab, Barcelona, Spain) at five sites: forehead, cheek, chest, back of the hand and tip of the index finger, held in place with porous tape.

In all eight group 1 subjects and eight out of the ten group 2 subjects, venous blood was collected into heparinized tubes from a cannula inserted into an antecubital fossa vein. Samples were taken at rest, at the end of 9 min of exercise and 10 min post-exercise for measurement of plasma catecholamines (noradrenaline, adrenaline and dopamine), glucose, insulin, c-peptide and renin and serum growth hormone. Additional catecholamine samples were taken at 3 and 6 min of exercise. EGTA and glutathione were added to the catecholamine samples to prevent oxidation. Trasylol was added to the growth hormone samples. The samples were kept on ice until centrifugation, and the plasma was then kept at −20°C until the following assays were performed. Plasma noradrenaline, adrenaline and dopamine were measured by HPLC with an electrochemical detector [13]. Plasma glucose levels were measured by the glucose oxidase method using a Chem Lab continuous flow autoanalyzer, plasma insulin was measured by radioimmunoassay using an RSL 125I-insulin kit (ICN Biomedicals, Inc., Thame, Oxon, U.K.) and serum growth hormone was measured with an I-labelled growth hormone immuno-radiometric assay kit (NETRIA; North East Thames Radioimmunoassay, London, U.K.).

Statistics

Results are expressed as means ± SEM. Statistical analysis of the subjects with and without treatment.
was performed using analysis of variance with the repeated measures design; correction factors were then applied for multiple comparisons (Minitab data analysis software, Inc. 1989). A P value of < 0.05 was considered significant. Non-significant changes are expressed as NS.

RESULTS

Results were analysed separately for the two groups; in group 1, eight subjects were given octreotide 120 min before exercise, and in group 2, ten subjects were given octreotide 60 min before exercise. In the pre-exercise period, to aid comparisons between the two groups, the time is provided in relation to the onset of exercise (OE). In addition, in brackets, times listed in both phases are in minutes after octreotide in the on phase, and at the equivalent period in the off phase. For the BP results, the two P values are for SBP and DBP.

Haemodynamic changes

Blood pressure. In group 1, supine BP before exercise was slightly higher on octreotide (159 ± 8/94 ± 4 mmHg off and 168 ± 7/97 ± 4 mmHg on, -30 E (90 min post-octreotide), P < 0.05 and NS; 158 ± 7/91 ± 3 mmHg off and 162 ± 8/98 ± 4 mmHg on, 0 E (120 min post-octreotide), P < 0.05 and NS) (Fig. 1). On standing, BP fell in both phases; the majority were unable to stand for 5 min when off treatment, and therefore data are given at 2 min of standing only in both phases. On standing at -30 E (90 min post-octreotide), BP was higher with octreotide (96 ± 4/62 ± 5 mmHg off and 113 ± 5/72 ± 4 mmHg on, each P < 0.05). With exercise (commenced 120 min after octreotide), BP fell to a similar level in both phases (to 142 ± 4/81 ± 3 mmHg off and 141 ± 6/83 ± 6 mmHg on, at the end of 9 min of exercise, NS). The overall fall in BP for the 9 min of supine exercise was also similar with and without octreotide. In the 10 min post-exercise period, cumulative supine BP was higher on octreotide (P < 0.001 for SBP and DBP), and the overall recovery in BP towards pre-exercise levels was faster (P < 0.05 and P < 0.005). On standing, 10 min post-exercise, BP was higher on octreotide (74 ± 3/45 ± 3 mmHg off and 83 ± 5/54 ± 4 mmHg on, each P < 0.05). Six of the subjects had an improvement in their postural symptoms pre-exercise and five had an improvement post-exercise.

In group 2, supine BP before exercise was higher on octreotide (154 ± 10/89 ± 5 mmHg off and 168 ± 6/96 ± 2 mmHg on, -30 E (30 min post-octreotide), each P < 0.05; 152 ± 10/90 ± 4 mmHg off and 166 ± 8/93 ± 3 mmHg on, 0 E (60 min post-octreotide), P < 0.05 and NS) (Fig. 1). On standing, BP fell in both phases, and as in group 1, the majority were unable to stand for 5 min when off octreotide, and therefore data are only given at 2 min of standing. Standing BP pre-exercise was higher with octreotide (82 ± 5/47 ± 3 mmHg off and 120 ± 11/70 ± 7 mmHg on, each P < 0.005). With exercise (commenced 60 min after octreotide), BP fell to a similar level both off and on octreotide (to 123 ± 8/67 ± 3 mmHg off and 128 ± 7/71 ± 3 mmHg on, at the end of 9 min of exercise, NS). The overall fall in SBP for the 9 min of supine exercise was larger post-octreotide (P < 0.0005). In the 10 min post-exercise period, cumulative supine BP was higher on octreotide (P < 0.0005 and P < 0.01), but the overall recovery in BP towards pre-exercise levels was similar in the two phases. On standing, 10 min post-exercise, BP was higher on octreotide (73 ± 5/44 ± 3 mmHg off and 87 ± 8/53 ± 5 mmHg on, each P < 0.05). Eight of the subjects had an improvement in their postural symptoms pre-exercise and six had an improvement post-exercise.

Heart rate. In group 1, there were no statistical differences in heart rate between the two phases. In group 2, cumulative heart rate was lower on octreotide (P < 0.01), but corrected multiple t-tests did not show this to be significant at any particular time.

Stroke distance, cardiac index and index of vascular resistance. These measurements were performed
in group 2 only. Resting stroke distance and cardiac index were not significantly higher at 60 min [stroke distance 10.43 ± 0.95 cm and 11.08 ± 0.86 cm (NS), cardiac index 719 cm/min and 749 cm/min (NS)] (Fig. 2). Both stroke distance and cardiac index increased to a similar extent with exercise in both phases. Post-exercise, stroke distance and cardiac index were again similar, except at 5 min when both stroke distance and cardiac index were larger after octreotide. Calculated systemic vascular resistance was similar in both phases at rest, decreased to the same degree with exercise and returned to normal at a similar rate post-exercise.

Skin temperature

Skin temperatures recorded in group 2 over the forehead, cheek and chest were similar off and on octreotide, and there were no significant changes with exercise. Over the finger, resting skin temperature was higher 60 min after octreotide (0E). With exercise, finger skin temperature decreased both off (26.15 ± 1.10°C to 25.43 ± 0.95°C, \( P < 0.05 \)) and on octreotide (28.20 ± 0.80°C to 27.12 ± 0.69°C, \( P < 0.005 \)), with a further fall on stopping exercise (to 25.20 ± 0.84°C off and 26.73 ± 0.73°C on octreotide, \( P < 0.01 \) and \( P < 0.005 \) respectively). During the whole study, finger skin temperature was higher on octreotide compared with off octreotide (\( P < 0.0001 \)). On the dorsum of the hand, skin temperature also decreased off (27.91 ± 0.75°C to 27.61 ± 0.71°C, \( P < 0.05 \)) and on octreotide (28.79 ± 0.45°C to 28.36 ± 0.49°C, \( P < 0.01 \)), with a further fall post-exercise (to 27.40°C off and 28.13°C on octreotide, \( P < 0.01 \) and \( P < 0.005 \) respectively). Overall, skin temperature was higher on octreotide (\( P < 0.05 \)).

Biochemical and hormonal changes

Venous plasma noradrenaline, adrenaline and renin activity levels did not change with exercise in either group 1 or 2, and levels were similar at rest, during exercise and post-exercise off and on octreotide (Tables 1 and 2).

Plasma insulin levels did not change with exercise, but in group 1 were lower with octreotide before, during and after exercise. In group 2, insulin levels were similar at rest (30 min post-octreotide), but were suppressed by octreotide at the end of exercise (70 min post-octreotide, \( P < 0.05 \)) and 10 min post-exercise (\( P < 0.05 \)). Serum growth hormone levels were not significantly lower on octreotide in either group and did not change with exercise in either phase. Plasma glucose was higher on octreotide before and at the end of exercise and post-exercise in group 2. A rise in plasma glucose only occurred with exercise in group 2 on octreotide.

DISCUSSION

This study with octreotide has confirmed previous observations on postural hypotension and provided new information on exercise-induced hypotension in primary AF. After octreotide there was a pressor response. Octreotide decreased postural hypotension
Effect of octreotide on exercise-induced hypotension

Table 1. Plasma venous noradrenaline, adrenaline, renin activity, insulin, glucose and serum growth hormone levels before, during and after exercise, on no treatment and on exercise 120 min after octreotide. Levels did not change significantly with exercise. P values indicate significant differences between the two phases.

<table>
<thead>
<tr>
<th></th>
<th>At rest (supine)</th>
<th>Exercise (min)</th>
<th>Post-exercise</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Noradrenaline (pg/ml)</td>
<td>No treatment</td>
<td>207 ± 55</td>
<td>210 ± 54</td>
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<td></td>
<td>Octreotide</td>
<td>152 ± 36</td>
<td>154 ± 44</td>
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<tr>
<td>Adrenaline (pg/ml)</td>
<td>No treatment</td>
<td>31 ± 6</td>
<td>13 ± 4</td>
</tr>
<tr>
<td></td>
<td>Octreotide</td>
<td>35 ± 7</td>
<td>28 ± 7</td>
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<tr>
<td>Plasma renin activity (pg h⁻¹ ml⁻¹)</td>
<td>No treatment</td>
<td>887 ± 141</td>
<td>—</td>
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<tr>
<td></td>
<td>Octreotide</td>
<td>1061 ± 232</td>
<td>—</td>
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<tr>
<td>Insulin (µ-units/l)</td>
<td>No treatment</td>
<td>8.7 ± 1.4</td>
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<td></td>
<td>Octreotide</td>
<td>4.9 ± 1.2</td>
<td>—</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>No treatment</td>
<td>5.0 ± 0.2</td>
<td>—</td>
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<tr>
<td></td>
<td>Octreotide</td>
<td>6.1 ± 0.4</td>
<td>—</td>
</tr>
<tr>
<td>Growth hormone (µ-units/l)</td>
<td>No treatment</td>
<td>3.3 ± 1.1</td>
<td>—</td>
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<td></td>
<td>Octreotide</td>
<td>2.6 ± 0.6</td>
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Table 2. Plasma venous noradrenaline, adrenaline, renin activity, insulin, glucose and serum growth hormone levels before, during and after exercise, on no treatment and on exercise 60 min after octreotide. Levels did not change significantly with exercise, except for an increase in plasma glucose with exercise after octreotide. P values indicate significant differences between the two phases.

<table>
<thead>
<tr>
<th></th>
<th>At rest (supine)</th>
<th>Exercise (min)</th>
<th>Post-exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Noradrenaline (pg/ml)</td>
<td>No treatment</td>
<td>119 ± 29</td>
<td>99 ± 23</td>
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<td></td>
<td>Octreotide</td>
<td>111 ± 26</td>
<td>107 ± 24</td>
</tr>
<tr>
<td>Adrenaline (pg/ml)</td>
<td>No treatment</td>
<td>24 ± 6</td>
<td>17 ± 2</td>
</tr>
<tr>
<td></td>
<td>Octreotide</td>
<td>25 ± 8</td>
<td>20 ± 12</td>
</tr>
<tr>
<td>Plasma renin activity (pg h⁻¹ ml⁻¹)</td>
<td>No treatment</td>
<td>1221 ± 427</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Octreotide</td>
<td>1024 ± 752</td>
<td>—</td>
</tr>
<tr>
<td>Insulin (µ-units/l)</td>
<td>No treatment</td>
<td>8.1 ± 1.2</td>
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<tr>
<td></td>
<td>Octreotide</td>
<td>8.0 ± 1.7</td>
<td>—</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>No treatment</td>
<td>5.0 ± 0.1</td>
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<td></td>
<td>Octreotide</td>
<td>5.3 ± 0.2</td>
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<tr>
<td>Growth hormone (µ-units/l)</td>
<td>No treatment</td>
<td>4.1 ± 1.3</td>
<td>—</td>
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<tr>
<td></td>
<td>Octreotide</td>
<td>2.5 ± 0.6</td>
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in the fasted state, when given 30 min and, to a lesser extent, 90 min before standing; however, it did not reduce the BP fall caused by supine exercise. Post-exercise, the BP was higher on than off octreotide, although the rate of recovery towards resting values was significantly faster only in group 1, given octreotide 120 min earlier. After octreotide, standing BP levels were higher, with fewer symptoms, than without treatment.

Octreotide inhibits the release of various peptides. In AF, splanchnic vasodilatation, without adequate compensatory vasoconstriction and cardiac changes, probably contributes to post-prandial hypotension [14]. Preventing peptide-induced splanchnic vasodi-
latation probably explains how octreotide reduces post-prandial hypotension [15]. Its mode of action in improving postural hypotension, however, is uncertain. There was a greater suppression of the potential vasodilator insulin at rest in group 1, but the postural BP fall pre-exercise was more severe than in group 2. This suggests that inhibition of vasodilatory peptide release was not the cause of the improvement in postural BP. A direct vasoconstrictor effect, as based on an increase in forearm vascular resistance, has been suggested [16], although this was not confirmed by other studies [17]. In the present study, forearm blood flow was not measured; there was no change in cardiac index and calculated systemic vascular resistance after octreotide at rest. However, finger skin temperature, for reasons which are unclear, was higher at all stages after octreotide.

Octreotide did not reduce the BP fall with supine exercise. The extent of the fall in group 2 was greater after octreotide, although the levels of BP reached in both groups after 9 min of exercise were similar. As the lack of improvement occurred whether exercise was performed 60 or 120 min after octreotide, a waning pharmacological effect was unlikely. Furthermore, insulin was suppressed in both groups after octreotide, suggesting adequate biological effects. In normal man, exercise causes vasodilatation in active skeletal muscle [18], and BP is maintained by an increase in cardiac output, constriction in other vascular beds and the effects of circulating substances, including noradrenaline and adrenaline. In AF, during exercise, there is a similar increase in cardiac index to that in normal subjects, but a greater fall in calculated systemic vascular resistance, suggesting that inadequate compensatory vasoconstriction accounts for the fall in BP [1–3]. Previous studies have not compared blood flow changes in exercising muscle in AF subjects and matched control subjects.

Vasodilatation in exercising skeletal muscle is likely to be due to the release of local metabolites, although factors such as potassium ions, opioids, nitric oxide and prostaglandins may play a part [19, 20]; the release of these vasodilators does not appear to be affected by octreotide. Octreotide suppresses the release of certain vasodilatory peptides. However, its inability to reduce exercise-induced hypotension suggests that circulating levels of such peptides do not contribute to the fall in BP. Our studies were performed in the fasted state when vasodilatory gastrointestinal peptides were not expected to be elevated; if exercise had followed food, octreotide may have had a beneficial effect.

Although the actual level to which BP fell with exercise in the octreotide and non-octreotide phases was similar, the degree of fall was greater after octreotide when given 60 min previously. The reasons for this are unclear. The pre-exercise BP level was higher after octreotide, and this may be related to its initial, presumed direct, pressor action which occurs in AF but not in normal subjects. In a previous study in AF, after 50 μg of octreotide, supine BP returned to basal levels after approximately 80 min [17]. This may explain the higher pre-exercise BP, with the apparently greater BP fall with exercise resulting from a waning of the initial pressor effect. In group 1, where there was more time (120 min) for BP to return to baseline, this effect was not seen. Other possibilities for the greater fall in group 2, studied earlier at 60 min, include suppression of vasoconstrictor peptides released by exercise.

Post-exercise, the BP was higher on octreotide, when given both 60 and 120 min before exercise. The rate of BP recovery to pre-exercise levels was faster in group 1 only, who exercised 120 min after octreotide. This did not occur in group 2, who exercised 60 min after octreotide, probably because, as discussed above, the pre-exercise BP was elevated by its initial pressor response. In the octreotide phase, the higher levels of BP post-exercise are probably of greater clinical relevance. These levels were associated with an increase in cardiac index; this was less likely to be due to a direct inotropic action. Somatostatin has a vasoconstrictor effect [21] which may also apply to its analogue octreotide. Increased venous return due to vasoconstriction may have raised cardiac output; this could be important immediately post-exercise when skeletal muscle pump activity ceases. The BP responses were not related to effects on the release of vasopressor substances such as noradrenaline, adrenaline or angiotensin II (as assessed by renin levels), as these were unchanged after octreotide at all stages (before, during and after exercise).

In this study, exercise increased the degree and symptoms of postural hypotension; this was similar to the effects reported previously with food ingestion [22]. This aggravation of postural hypotension was reduced by octreotide when assessed 10 min post-exercise. It is not known if its beneficial effects would have been more pronounced if the subjects had stood earlier, when the post-exercise supine BP was higher than in the non-octreotide phase. These findings may explain the improvement in walking time reported in a previous study [7], but where the mechanisms were uncertain as BP was not recorded during or after exercise. The precise reasons for the improvement in postural hypotension post-exercise were unclear, and may include a putative vasoconstrictor effect of octreotide. In AF, lack of splanchnic vasoconstriction contributes to postural hypotension [23], and the ability of octreotide to reduce splanchnic blood flow may have been additionally beneficial during postural change.

In conclusion, in fasted AF subjects, octreotide did not reduce exercise-induced hypotension. Although in one group it increased the fall in BP with exercise, the lowest level of BP in both groups was similar to the non-octreotide phase. After octreotide, lying and standing BP were higher both
before and after exercise. Octreotide-sensitive vasodilatory peptides, therefore, do not appear to play a major role in lowering BP during exercise. The mechanism by which octreotide aided BP recovery after exercise and reduced postural hypotension remains unclear.

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REFERENCES