Cardiovascular and catecholamine changes induced by supine exercise and upright posture in vasovagal syncope

Comparisons with normal subjects and subjects with sympathetic denervation

G. D. P. Smith, L. P. Watson and C. J. Mathias

The haemodynamic and catecholamine responses to supine leg exercise were studied in vasovagal syncope (n = 10), pure autonomic failure (n = 10) and in control (n = 10) subjects.

With exercise, blood pressure increased in controls; with a smaller rise in vasovagal syncope, and a substantial fall in pure autonomic failure. Heart rate increased similarly in controls and vasovagal syncope, but less in pure autonomic failure. The increase in cardiac index was less in controls and pure autonomic failure than vasovagal syncope; the fall in systemic vascular resistance was greatest in pure autonomic failure, but also fell more in vasovagal syncope than controls. Plasma noradrenaline levels increased in controls; with a smaller rise in vasovagal syncope and no increase in pure autonomic failure. Plasma adrenaline levels increased in vasovagal syncope only. The blood pressure responses to standing before and after exercise were similar in controls and vasovagal syncope, with no postural blood pressure fall; in pure autonomic failure there was a greater postural blood pressure fall post exercise.

In conclusion, with supine exercise, blood pressure rose in controls and vasovagal syncope, and fell in pure autonomic failure. Systemic vascular resistance fell more in vasovagal syncope and pure autonomic failure, than controls. Noradrenaline responses differed and adrenaline rose in vasovagal syncope only. Standing post exercise did not induce syncope in vasovagal syncope, but increased postural hypotension in pure autonomic failure. There are clear differences in response to exercise in vasovagal syncope and pure autonomic failure. The differences between vasovagal syncope and control subjects suggest an underlying abnormality which may predispose to vasodepression in subjects with vasovagal syncope.

Key Words: Exercise, vasovagal syncope, autonomic failure, blood pressure, catecholamine.
was performed to evaluate whether it would lower blood pressure or precipitate a vasovagal episode in vasovagal syncope. Comparisons have been made with normal subjects (controls), and subjects with pure autonomic failure, to determine similarities and differences.

**Methods**

Ten subjects with recurrent vasovagal syncope (five male, mean age 34, range 19–54) were studied. All had a typical history of vasovagal syncope, with no symptoms, signs or investigations suggestive of ischaemic heart disease, aortic stenosis, hypertrophic cardiomyopathy, or diabetes mellitus. Detailed investigations and autonomic function testing\(^9\) to assess sympathetic and parasympathetic cardiac pathways, excluded primary or secondary autonomic failure. There was no postural hypotension on standing or during initial 45° head-up tilt on the tilt table. Prolonged tilt or provocative stimuli, such as venesection, induced classical vasovagal syncope, with bradycardia and hypotension, in five of the subjects.

The responses in vasovagal syncope were compared with those in 10 healthy normal subjects (controls, four male, mean age 37, range 27–57 years), with no history of syncopal episodes and with normal autonomic function on testing; in addition, responses from 10 subjects with pure autonomic failure (six male, mean age 52, range 45–58 years) were compared. The pure autonomic failure subjects had postural hypotension, of more than 30 mmHg systolic blood pressure, with symptoms including dizziness, visual disturbances and fainting indicative of cerebral ischaemia during postural change. All had sympathetic vasoconstrictor failure on physiological testing\(^9\) with an impaired plasma noradrenaline response to head-up tilt. The majority of subjects also had evidence of cardiac parasympathetic impairment on testing. 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.

All studies were performed at 0900 h in a temperature-controlled clinical laboratory (average temperature 24 ± 2°C) after an overnight fast. The vasovagal syncope and control subjects were on no medication. In pure autonomic failure, medication (mainly fludrocortisone and desmopressin) was withdrawn the day before the study. A cannula was inserted into a vein in the antecubital fossa for blood sampling. Blood pressure and heart rate were recorded with an automated sphygmomanometer (Dinamap), which was calibrated against a mercury sphygmomanometer. Following 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 in the supine position by pedalling a cycle ergometer at workloads of 25, 50 and then 75 Watts, each for 3 min. Measurements were made at the end of each stage of exercise and continued for a further 10 min post exercise while supine. The responses to standing were 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\(^1\), to be the maximum level of exercise that the majority of these subjects could perform, while on no treatment. In four controls, four vasovagal syncope and seven pure autonomic failure, non-invasive finger blood pressure measurements, using the Finapres (Ohmeda), were made on a chart recorder at rest, at the end of each stage of exercise and post exercise; the data were averaged for 10 consecutive cardiac cycles at each stage.

The following additional measurements were made in the supine position at rest, at the end of each stage of exercise and post exercise; 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). A mean velocity of 20 consecutive cardiac cycles were taken for each observation. This technique has been validated as a measure of cardiac output at rest\(^1\) and with exercise\(^1\) and has been used previously with supine exercise\(^12,13\).

Mean arterial blood pressure was calculated from the diastolic blood pressure plus one-third of the pulse pressure, and index of systemic vascular resistance was calculated from mean arterial pressure/cardiac index. At 3, 6 and 9 min of exercise and 10 min post exercise, venous blood was collected into heparinized tubes with added 1,2-di-(2-aminomethoxy) ethan-N,N,N',N'-tetraacetic acid (EGTA) and glutathione to prevent oxidation. Samples were kept on ice until centrifuged and the plasma then kept at −20°C until assayed. Plasma noradrenaline, adrenaline and dopamine were measured by high performance liquid chromatography with an electrochemical detector\(^14\).

Results are expressed as means ± SEM. Statistical analyses were 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**

**Blood pressure**

Using the automated sphygmomanometer, resting supine blood pressure was similar in controls (121 ± 4/74 ± 4 mmHg) and vasovagal syncope (118 ± 4/73 ± 2 mmHg) but higher in pure autonomic failure (144 ± 5/90 ± 4 mmHg, each P<0.0001) (Table 1). As some pure autonomic failure subjects were unable to remain standing for 5 min, especially after exercise, only data after 2 min of standing are provided. On standing pre exercise, blood pressure was similar in controls
vasovagal syncope, at rest 127 ± 12/68 ± 8 mmHg, with exercise 150 ± 12/83 ± 7, 166 ± 12/90 ± 8 and 180 ± 14/100 ± 8 mmHg at 3, 6 and 9 min and post exercise 137 ± 16/70 ± 9, 133 ± 15/71 ± 8 and 131 ± 13/71 ± 7 mmHg at 2, 5 and 10 min. In vasovagal syncope, at rest 127 ± 12/68 ± 8 mmHg, with exercise 148 ± 13/82 ± 8, 163 ± 14/87 ± 8 and 175 ± 14/94 ± 9 mmHg at 3, 6 and 9 min and post exercise 135 ± 15/70 ± 9, 129 ± 14/71 ± 8 and 126 ± 13/72 ± 7 mmHg at 2, 5 and 10 min. In pure autonomic failure, at rest 149 ± 9/89 ± 5 mmHg, with exercise 146 ± 10/79 ± 5, 135 ± 10/77 ± 7 and 127 ± 11/67 ± 7 mmHg at 3, 6 and 9 min and post exercise 136 ± 15/71 ± 9, 147 ± 15/79 ± 8 and 146 ± 11/89 ± 6 mmHg at 2, 5 and 10 min. The blood pressure trends measured with the Finapres were, therefore, similar to those measured with the automated sphygmomanometer, in each group.

Heart rate

Heart rate in controls, vasovagal syncope and pure autonomic failure was similar at rest (70 ± 3, 66 ± 3 and 69 ± 4 beats . min⁻¹) and after standing pre exercise (85 ± 6, 81 ± 4 and 80 ± 3 beats . min⁻¹). At the end of 9 min of exercise heart rate was higher in controls (116 ± 4 beats . min⁻¹) and vasovagal syncope (114 ± 7 beats . min⁻¹) than pure autonomic failure (88 ± 2 beats . min⁻¹, each P<0.001) (Fig. 1). After exercise, heart rate rapidly decreased towards baseline in all three groups and increased to a similar level on standing (to 90 ± 6, 92 ± 4 and 85 ± 3 beats . min⁻¹, respectively).

Stroke distance, cardiac index and index of systemic vascular resistance

Assessment of stroke volume and cardiac output depend on aortic diameter, which was not measured. Basal stroke distance and cardiac index values, therefore, have not been compared among the three groups. The percentage change in stroke distance and cardiac index are independent of aortic diameter and, therefore, have been compared during and post exercise (Fig. 2). With

<table>
<thead>
<tr>
<th>Systolic blood pressure (mmHg)</th>
<th>Pre exercise</th>
<th>Supine exercise</th>
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<tr>
<td></td>
<td>Lying</td>
<td>3 min</td>
<td>6 min</td>
<td>9 min</td>
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<tr>
<td>Controls</td>
<td>121 ± 4</td>
<td>133 ± 4*</td>
<td>141 ± 4**</td>
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<tr>
<td>VVS</td>
<td>118 ± 4</td>
<td>130 ± 4*</td>
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Diastolic blood pressure (mmHg)

|                                | Lying       | 3 min          | 6 min        | 9 min    |
| Controls                       | 85 ± 7**    | 80 ± 3         | 88 ± 3*      | 97 ± 4** |
| VVS                            | 73 ± 2      | 80 ± 4*        | 84 ± 4**     | 87 ± 2** |
| PAF                            | 90 ± 4      | 83 ± 4         | 73 ± 3**     | 70 ± 3** |
|                                | Standing    | 71 ± 4         | 72 ± 4       | 75 ± 4   |
|                                |             | 81 ± 5         |              |          |

Heart rate

Heart rate in controls, vasovagal syncope and pure autonomic failure was similar at rest (70 ± 3, 66 ± 3 and 69 ± 4 beats . min⁻¹) and after standing pre exercise (85 ± 6, 81 ± 4 and 80 ± 3 beats . min⁻¹). At the end of 9 min of exercise heart rate was higher in controls (116 ± 4 beats . min⁻¹) and vasovagal syncope (114 ± 7 beats . min⁻¹) than pure autonomic failure (88 ± 2 beats . min⁻¹, each P<0.001) (Fig. 1). After exercise, heart rate rapidly decreased towards baseline in all three groups and increased to a similar level on standing (to 90 ± 6, 92 ± 4 and 85 ± 3 beats . min⁻¹, respectively).

Stroke distance, cardiac index and index of systemic vascular resistance

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exercise, stroke distance did not change in controls 
(−6 ± 4%, ns) and vasovagal syncope (+9 ± 7% ns), but 
increased in pure autonomic failure (25 ± 7%, P<0.005). 
Cardiac index increased with exercise in all three groups 
(61 ± 10%, 88 ± 17% and 58 ± 7%, each P<0.001); the 
increase in vasovagal syncope was not significantly 
greater than in controls or pure autonomic failure. 
With exercise, calculated systemic vascular resistance 
decreased in controls (by 15 ± 6%, P<0.05), vasovagal 
syncope (by 31 ± 6%, P<0.005), and pure autonomic 
failure (by 40 ± 5%, P<0.05) with a significantly smaller 
fall in controls compared with vasovagal syncope 
(P<0.05) or pure autonomic failure (P<0.005).

**Plasma catecholamines**

Resting venous plasma noradrenaline concentration was 
similar in controls (260 ± 54 pg . ml⁻¹) and vasovagal

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**Figure 1** Changes in systolic and diastolic blood pressure (SBP and DBP) and heart rate (HR), during and after supine exercise; in normal (controls), vasovagal (VVS) and pure autonomic failure (PAF) subjects.

Significant changes from baseline: *P<0.05 and **P<0.001.
Figure 2 Percentage change in stroke distance, cardiac index and systemic vascular resistance (SVR) during and after supine exercise; in normal (controls), vasovagal (VVS) and pure autonomic failure (PAF) subjects.

Significant changes from baseline: *P<0.05 and **P<0.001.

Resting venous plasma adrenaline concentration was similar in controls (28 ± 5 pg. ml⁻¹), vasovagal syncope (31 ± 6 pg. ml⁻¹) and pure autonomic failure (20 ± 5 pg. ml⁻¹). With exercise, adrenaline did not change in controls (to 27 ± 3 pg. ml⁻¹), but increased in vasovagal syncope (to 63 ± 14 pg. ml⁻¹, P<0.05); the response was significantly different between the two groups (P<0.05). There was no change in adrenaline in
Figure 3 Plasma noradrenaline (NA) and adrenaline (A) during and after supine exercise; in control, vasovagal (VVS) and pure autonomic failure (PAF) subjects. Significant changes from baseline: *P<0.05 and **P<0.001.

Discussion

Our study has demonstrated clear haemodynamic and catecholamine differences between the vasovagal syncope, control and pure autonomic failure subjects. With exercise, the blood pressure response was initially similar in vasovagal syncope and controls: by the end of exercise, however, the increase in mean arterial pressure was smaller in vasovagal syncope. Their blood pressure response, and those of the controls, differed markedly from pure autonomic failure, in whom there was substantial exercise induced hypotension. In all our subjects blood pressure was measured using an automated sphygmomanometer. Movement artifact is possible during exercise, but this is reduced if the arm is held still.
during measurements\cite{15}, which was the case with our study. In comparison with inter-arterial recordings, sphygmomanometer measurements indicate a smaller increase in systolic blood pressure with exercise\cite{16}. Underestimation of systolic blood pressure, however, should have applied to both control and vasovagal subjects, and it was unlikely that a significant difference in blood pressure responses was missed. Moreover, although analysis of blood pressure data recorded with the Finapres technique in the controls and vasovagal syncope indicated a higher systolic blood pressure and marginally lower diastolic blood pressure at rest and a larger systolic and diastolic blood pressure increase with exercise, than using the automated sphygmomanometer readings (which is similar to the findings reported previously in normal subjects\cite{17}), the difference between the control and vasovagal syncope groups was not more obvious. In pure autonomic failure, the markedly different blood pressure response to the controls and vasovagal syncope on sphygmomanometry, was reflected in the Finapres recordings. Therefore, were consistent with the trends in blood pressure with different phases of exercise as measured by sphygmomanometry in the different groups.

Cardiac index increased more in vasovagal syncope than controls or pure autonomic failure. There was a larger fall in systemic vascular resistance in vasovagal syncope than controls, with the largest fall in pure autonomic failure. The catecholamine responses to exercise also differed; vasovagal syncope had a smaller increase in noradrenaline than controls, with no increase in pure autonomic failure. Levels of adrenaline did not change with exercise in controls or pure autonomic failure, but rose in vasovagal syncope. On standing, there was no blood pressure fall in controls or vasovagal syncope, and blood pressure was the same pre and post exercise. In pure autonomic failure, however, postural hypotension was larger post exercise.

In vasovagal syncope, symptoms occur intermittently and there is usually no sustained abnormality on routine autonomic function testing, apart from bradycardia and hypotension on prolonged tilt, which occurs in 30–50% of subjects\cite{18,19}. The bradycardia results from increased cardiac vagal activity, while the fall in blood pressure appears secondary to vasodilatation resulting from withdrawal of sympathoneural activity\cite{20}. Hypotension may occur even if the heart rate is maintained by vagal blockade with atropine\cite{21} or by demand cardiac pacemaker\cite{22}. The precise reasons for the initiation of a vasovagal episode are unclear. In some cases central activation, induced by apprehension and fear, or other factors, is causative. It has been hypothesized that a pathway descending from the cortical and hypothalamic centres to medullary cardiovascular centres is triggered by such emotional events\cite{23}. An alternative peripheral pathway is thought to originate in the heart, and involve afferent sensory pathways from mechanoreceptors in the ventricles\cite{24}. Typical vasovagal episodes, however, occur following cardiac transplantation\cite{25} and such events, therefore, may occur independently of ventricular baroreceptor activity. Impulses arising from veno-atrial stretch receptors in the walls of underfilled atria and great veins, which are left intact during transplantation, have been suggested as an alternative explanation\cite{26}.

One of the difficulties in diagnosis and evaluation of therapy in vasovagal syncope is in initiating a vasovagal response in the laboratory. In 30–67% of subjects with suspected vasovagal syncope an episode is induced by prolonged head-up tilt\cite{18,19}. Pharmacological approaches using isoprenaline\cite{27,28}, nitrovasodilators\cite{29}, bromocriptine\cite{30} and adenosine\cite{31} have also been used. A combination physiological approach using both head-up tilting and simultaneous lower body negative suction has the advantage of avoiding drugs, although presyncope was also induced in normal subjects\cite{32}. A fall in blood pressure with exercise has been reported to cause vasodepressor syncope in five subjects\cite{2}. In four the responses to tilt table testing were also highly suggestive of a vasovagal aetiology. This raised the possibility of whether exercise, with its multitude of effects on both neural activation and hormonal release, may predispose such subjects to syncope. In a study of subjects with syncope during or within 1 min of stopping exertion, two subjects had structural heart disease, out of the other 10 subjects studied, nine had tilt-induced hypotension-bradycardia\cite{33}. This again suggested that exercise can be a precipitating cause of syncope in subjects with vasovagal syncope. In our vasovagal syncope subjects, however, exercise did not induce a vasodepressor response, either when supine (to avoid the confounding effects of posture), or on standing post exercise. There were, however, haemodynamic and hormonal differences from controls, as will be discussed later. The results in vasovagal syncope were in marked contrast, however, with pure autonomic failure with sympathetic denervation, and a marked fall in blood pressure.

Hypotension during exercise may result from other factors, which include structural heart disorders due to severe coronary artery disease\cite{34,35}, aortic stenosis\cite{36} or hypertrophic cardiomyopathy\cite{37}. These factors could not have contributed to the abnormal responses in vasovagal syncope, or to the severe exercise-induced hypotension in pure autonomic failure, as they were excluded. In pure autonomic failure, exercise-induced hypotension probably results from vasodilatation in exercising muscle, with a fall in peripheral vascular resistance not counteracted by compensatory changes, because of the sympathetic defect\cite{38}. This has been demonstrated in sympathetic failure of either central (Shy-Drager syndrome\cite{39}), or peripheral origin (pure autonomic failure\cite{40,41}). Hypotension may also occur with upright exercise in diabetes mellitus with autonomic neuropathy, although it was not clear if cardiac impairment, due to diabetic cardiomyopathy, may have contributed\cite{42}.

With exercise, vasovagal syncope had a smaller increase in mean arterial blood pressure than controls. As the subjects’ oxygen consumption was not recorded it
is possible that the difference was due to a different relative workload. This is unlikely as their heart rate responses to the exercise protocol were similar. The vasovagal syncope subjects also had a greater increase in cardiac index and a larger fall in systemic vascular resistance than in controls favouring a greater degree of peripheral vasodilatation. This is consistent with findings of an abnormal fall in forearm vascular resistance demonstrated in vasodepressor syncope during supine bicycle exercise. In pure autonomic failure the fall in systemic vascular resistance was greater than in vasovagal syncope, presumably because of their marked inability to vasoconstrict because of sympathetic denervation. In vasovagal syncope, vasodepression mainly results from withdrawal of sympathetic neural activity. A subnormal increase in sympathetic activity, as suggested by the smaller than normal increase in noradrenaline, may account for the abnormal fall in systemic vascular resistance with exercise in vasovagal syncope. Other factors, however, including abnormal humoral release, need considering. Plasma catecholamine changes preceding vasovagal syncope have been described, but with much variation in different studies. An initial rise in plasma noradrenaline may occur immediately preceding syncope, followed by a stable or declining level during the vasovagal response. In contrast, plasma adrenaline often higher during syncope and a progressive increase in adrenaline has been demonstrated preceding syncope. In the present study there was a subnormal rise in plasma noradrenaline associated with the fall in systemic vascular resistance, suggesting a smaller degree of sympathetic neural activity. Furthermore, plasma adrenaline levels were higher at the end of exercise in vasovagal syncope, and the increase appeared to precede the fall in systemic vascular resistance. Elevated adrenaline may have caused vasodilatation through stimulation of β-adrenergic receptors. Syncope, however, did not occur in our vasovagal syncope subjects and it may be that a greater increase in plasma adrenaline was needed, as is known to occur with more strenuous levels of exercise in the upright position. The data from our study favours a lower threshold for the release of adrenaline with exercise in vasovagal syncope, for reasons which are currently not known. The differences in venous noradrenaline and adrenaline responses, however, could also have been due to an increase in forearm muscle blood flow, as this has been demonstrated with supine exercise in vasovagal syncope. Arterial or arterialized venous blood sampling would be needed to exclude this possibility. In pure autonomic failure the responses were markedly different from controls and vasovagal syncope; they had abnormally low noradrenaline, both before and during exercise, consistent with a peripheral sympathetic neural defect. There was no change in adrenaline, excluding adrenal medullary activation and a humoral contribution to the blood pressure fall.

Finally, we determined the blood pressure and heart rate responses to standing before and after exercise. In controls there was no change, while in pure autonomic failure there was an accentuation of postural hypotension, with greater symptoms. This is presumably because of the additional load of gravity and peripheral pooling, in the absence of sympathetic vasoconstrictor activity. In dopamine β hydroxylase deficiency, in whom there is a severe sympathetic defect because of the inability to convert dopamine to noradrenaline and adrenaline, there is a marked accentuation of postural hypotension post exercise, despite having no change in supine blood pressure during exercise. We therefore assessed postural responses post exercise in vasovagal syncope, despite their lack of fall in blood pressure during exercise. In vasovagal syncope, however, standing post exercise did not induce either abnormal haemodynamic responses or symptoms of presyncope. It is unlikely, therefore, that the current exercise workload and protocol can be used to unmask vasodepression in vasovagal syncope.

In conclusion, our study suggested that subjects with vasovagal syncope have abnormal responses to supine exercise even in the absence of vasovagal episodes. They developed a larger than normal fall in systemic vascular resistance, which was associated with a subnormal increase in plasma noradrenaline and preceded by a greater release of plasma adrenaline. This supports the theory that the initiating event in a vasovagal episode is the abnormal release of adrenaline. This may indicate an intrinsic abnormality predisposing them, for reasons currently unclear, to a lower threshold for adrenaline release. A fall in blood pressure on tilt and with upright exercise may occur, as reported by Sneddon et al., in both vasovagal syncope and sympathetic denervation due to pure autonomic failure. In our studies, however, the haemodynamic and catecholamine responses to supine exercise were markedly different in vasovagal syncope and pure autonomic failure.

References


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