

# Exercise induced vasodepressor syncope

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## Abstract

**Five cases of exercise induced pure vasodepressor syncope in patients without significant structural heart disease are reported. Hypotension and symptoms of syncope or presyncope were induced by treadmill exercise testing and in each case limited exercise performance. Evidence of inappropriate peripheral vasodilatation, probably as a consequence of ventricular mechanoreceptor stimulation, was shown in all five patients. Head up tilt testing resulted in hypotension in four patients and isoprenaline infusion in the supine position resulted in hypotension in the fifth. These patients had a new condition of exercise induced neurally mediated (vasodepressor) syncope without appreciable structural cardiac abnormalities.**

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Exercise induced hypotension or syncope is often an ominous symptom of severe structural heart disease such as aortic stenosis, hypertrophic cardiomyopathy, and severe coronary artery disease, or it may be due to exercise induced tachyarrhythmias.<sup>1-3</sup> Symptomatic bradycardia and asystole, however, have been described after exercise in patients with normal hearts.<sup>4-7</sup> We report five cases of recurrent debilitating pure vasodepressor syncope or presyncope. The condition of recurrent exercise induced vasodepressor syncope has not previously been described in patients without appreciable structural heart disease.

## Case reports

### PATIENT 1

A 70 year old retired farmer presented with a 10 year history of presyncope on moderate exertion. His symptoms had progressed so that only moderate exertion was required to

induce light headedness and blurred vision, but he was able to stop exercise before complete syncope occurred. He was otherwise fit and well and clinical examination was unremarkable. A 12 lead electrocardiogram, cross sectional echocardiography, and coronary angiography were normal. A standard treadmill exercise test was performed with the Bruce protocol. He exercised for 13 minutes until the test was stopped because of presyncope (table). Despite a normal heart rate response (70-140 beats/min) the systolic blood pressure fell from 150 mm Hg to 80 mm Hg at peak exercise. A repeat exercise test resulted in a fall in systolic blood pressure to 40 mm Hg.

To ascertain the mechanism of hypotension the patient underwent an upright bicycle exercise test with invasive monitoring (figure). Presyncope occurred at eight minutes of exercise when the blood pressure was 39/26 mm Hg. The rise in cardiac output was appropriate but the dramatic fall in systemic vascular resistance resulted in profound hypotension.

The patient then underwent tilt testing with a drug free 60° tilt; presyncope with the same symptoms as those found during exercise occurred after 28 minutes of tilt with a vasodepressor response, the minimum blood pressure was 55/41 mm Hg. A repeat tilt was performed after  $\beta$  blockade with propranolol, which resulted in hypotension and presyncope at 21 minutes. Further tilt testing on two occasions while the patient was taking disopyramide (100 mg three times daily) yielded negative results with the patient tolerating 60 minutes of tilt on both occasions. He tolerated 13 minutes of exercise without hypotension while taking disopyramide and has remained symptom free without exercise limitation after three months of follow up.

### PATIENT 2

A 73 year old nurse presented with a two year history of exertional dizziness and three

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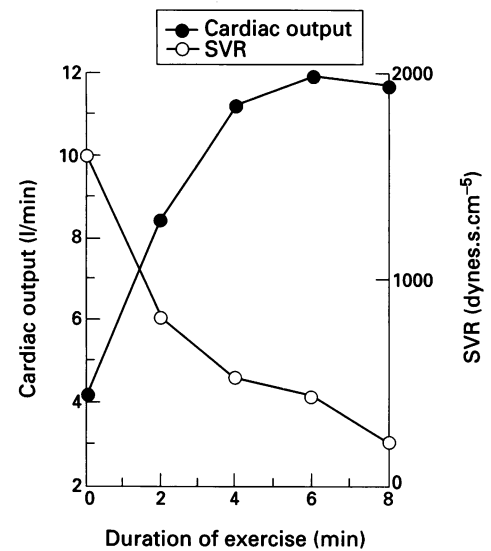
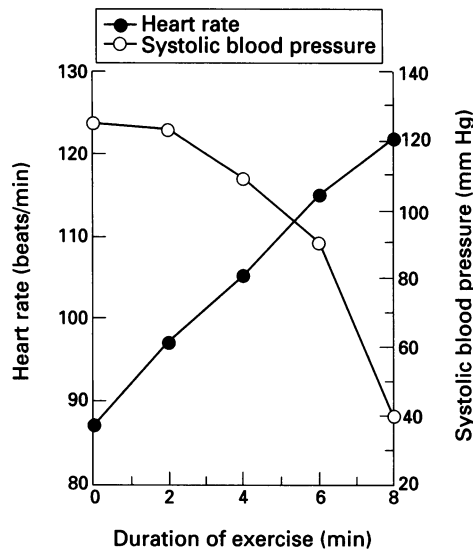
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## Summary of exercise and tilt data from all five patients

Patient No	Age (yr)	Exercise duration (mins)	Minimum systolic BP (mm Hg)	HR at minimum BP (beats/min)	Tilt result	Tilt duration (min)	Minimum systolic BP during tilt (mm Hg)	Reduction in FVR on supine exercise (%)	Drug treatment	Exercise test on treatment	Exercise duration on treatment (min:s)	Tilt test result on treatment	Tilt duration on treatment (min)
1	70	13	80	140	+ve	28	55	(SVR-84)	Disopyramide	-ve	13	-ve	60
2	73	3	<50	129	+ve	45	70	-11	Metoprolol	-ve	9:34	—	—
3	34	13:14	70	174	+ve	—	60	-48	Metoprolol	-ve	18:15	—	—
					(isoprenaline-supine)								
4	16	10	110	196	+ve	40	80 (HR 40)	-82	Disopyramide	—	—	-ve	45
5	16	15:30	85	180	+ve	20	60	-62	No Treatment	—	—	—	—

BP, blood pressure; FVR, forearm vascular resistance; HR, heart rate; min, minimum; SVR, systemic vascular resistance; +ve, positive; -ve, negative.

The results of invasive haemodynamic study in patient 1 during exercise induced hypotension. SVR, systemic vascular resistance.



episodes of syncope that occurred while walking. Physical examination was normal apart from modest hypertension of 160/110 mm Hg. Her resting electrocardiogram was normal and echocardiography showed mild concentric left ventricular hypertrophy (diastolic left ventricular wall thickness 13 mm). Cardiac catheterisation showed normal left ventricular function and selective coronary angiography showed a <30% stenosis in the mid left anterior descending artery but otherwise normal vessels. On an exercise test she tolerated only three minutes of the Bruce protocol stopping because of presyncope (table). She then became unconscious with no palpable pulse but a heart rate of 129 beats/min in sinus rhythm. She recovered consciousness with a blood pressure of 70/40 mm Hg and her heart rate fell to 42 beats/min after which she developed noticeable inferolateral ST segment depression but no chest pain. Two further exercise tests were performed with intra-arterial pressure monitoring to clarify the blood pressure changes leading to syncope. She exercised, however, for nine and 11 minutes of the Bruce protocol on these occasions with no symptoms apart from fatigue although there was a 20 mm Hg fall in systolic pressure at peak exercise compared with the resting value. During a symptom limited supine bicycle exercise test with measurement of forearm blood flow, forearm vascular resistance fell by 11% (44–39 arbitrary units) from baseline to peak exercise although the blood pressure and heart rate responses were appropriate (mean arterial pressure 102–112 mm Hg, heart rate 63–120 beats/min).<sup>8,9</sup> A tilt test at 60° for 45 minutes induced a fall in systolic pressure to 70 mm Hg with no bradycardia or symptoms. A repeat tilt with isoprenaline at doses up to 25 ng/kg/min again induced asymptomatic hypotension (systolic pressure 70 mm Hg).

As her exercise responses were poorly reproducible she was discharged on empirical treatment of metoprolol (50 mg twice daily). In the next two months she had one further syncopal attack. She has had no further syn-

cope after 10 months while taking metoprolol (100 mg twice daily) but remains prone to occasional exertional dizziness.

#### PATIENT 3

A 34 year old scaffolder presented after a syncopal attack that occurred while running up eight flights of stairs. He had been investigated when aged 25 after a similar episode that occurred while out running. In the intervening years he continued to have frequent presyncopal episodes associated with nasal congestion, nausea, and sweating all of which developed on exercise and necessitated his lying down for at least 20 minutes. Physical examination, electrocardiogram, and echocardiogram were normal. An exercise test with the Bruce protocol was ended at 13 minutes 14 seconds by the patient because he was aware of an attack developing (table). The blood pressure immediately after exercise was 70/30 mm Hg with a heart rate of 174 beats/min. Recovery took 20 minutes and necessitated a 500 ml intravenous infusion of colloid plasma expander. A repeat exercise test was ended at 15 minutes with similar hypotension (minimum systolic blood pressure 75 mm Hg) at peak exercise. An exercise test with invasive arterial pressure monitoring did not provoke any symptoms or hypotension (exercise duration 19 minutes 40 seconds). Supine exercise with measurement of forearm blood flow showed a profoundly abnormal response with flow increasing at peak exercise by 134% and forearm vascular resistance falling by 48% although the mean arterial pressure rose appropriately by 19 mm Hg.<sup>8,9</sup> A 45 minute 60° head up tilt was normal but an attempt to tilt him during an infusion of isoprenaline at a dose of 25 ng/kg/min resulted in profound hypotension in the supine position (systolic blood pressure 60 mm Hg, heart rate 120 beats/min) with exact reproduction of his usual symptoms.

He remained symptomatic on low dose  $\beta$  blockade, but treatment with metoprolol (150–200 mg daily) has prevented further syncope during 10 months of follow up and a

repeat exercise test on treatment was normal (exercise duration 18 minutes 15 seconds).

#### PATIENT 4

A 16 year old girl presented with a six year history of exercise induced syncope and presyncope that occurred reproducibly on running about 100 metres. Also, she had sustained three episodes of syncope after prolonged standing. On a treadmill exercise test, systolic blood pressure initially increased but fell from a maximum of 150 mm Hg at five minutes to 110 mm Hg at peak exercise (10 minutes). At this time she was aware of her usual premonitory symptoms and exercise had to be ended (table). A standard 60° head up tilt test resulted in presyncope at 40 minutes when her systolic blood pressure was 80 mm Hg and heart rate 40 beats/min. During supine exercise, systolic blood pressure climbed by 30 mm Hg but forearm vascular resistance fell from 65 at rest to 12 at peak exercise (arbitrary units). A trial of propranolol did not prevent exercise induced symptoms or tilt induced syncope. Disopyramide (100 mg three times daily) abolished her symptoms on exercise, however, and made her tilt negative. A repeat supine exercise test showed an increase in forearm vascular resistance from 53 at rest to 56 at peak exercise.

#### PATIENT 5

A 16 year old boy presented with a three month history of recurrent presyncope during strenuous physical activity with symptoms persisting for several minutes after the end of exercise. His electrocardiogram showed borderline left ventricular hypertrophy on voltage criteria but echocardiography at that time and subsequently at the age of 19 showed normal left ventricular wall thickness. On the treadmill, systolic blood pressure increased from 130 mm Hg at rest to 195 mm Hg at 15 minutes before falling abruptly to 130 mm Hg at 15.5 minutes with associated presyncopal symptoms (table). The stress test was ended and the first blood pressure recording early in recovery was 85 mm Hg with no bradycardia. On a tilt test, he developed presyncope at 20 minutes with a systolic blood pressure of 60 mm Hg and a minimum heart rate of 40 beats/min. His forearm vascular responses to supine exercise were abnormal with forearm vascular resistance falling at peak exercise by 62%. He elected not to have drug treatment and his symptoms have persisted during a three year follow up period.

### Discussion

We have described five patients with exercise induced vasodepressor syncope or presyncope whose symptoms could be induced by treadmill exercise testing.

Exercise induced hypotension has been described in a number of conditions, usually as a consequence of severe structural cardiac disease such as aortic stenosis, hypertrophic cardiomyopathy, and appreciable coronary artery disease.<sup>1-3</sup> In all these situations inap-

propriate vasodilatation, resulting from ventricular mechanoreceptor stimulation has been implicated.<sup>8-10</sup> Exercise induced neurally mediated syncope (vasovagal syncope) leading to profound bradycardia or asystole in patients with normal hearts has also been described.<sup>4-7</sup> In one large study, hypotension after maximal exercise testing has been documented in 3.1% of 781 asymptomatic volunteers aged <55 years.<sup>11</sup> None developed syncope and in most cases hypotension occurred at least four minutes after the end of exercise. In none of this large series was exercise ended as a result of presyncope or hypotension. The particularly unusual feature of our patients was that hypotension and symptoms of presyncope developed during rather than after exercise and were the main reason for stopping exercise. In patients 2 and 3 it is also of note that the exercise response was not reproducible so that on occasions when hypotension did not intervene their exercise duration and workload were substantially greater.

The invasive haemodynamic study performed on patient 1 showed that hypotension was not due to a fall in cardiac output but was due to inappropriate vasodilatation, a similar mechanism to that seen in hypertrophic cardiomyopathy.<sup>12</sup> Abnormal control of peripheral vascular tone was also shown in patients 2-5 by their inability to vasoconstrict the non-exercising limbs during supine exercise; an abnormal response that has been previously documented in patients with aortic stenosis and hypertrophic cardiomyopathy.<sup>8,9</sup> Tilt tests, a well accepted means of provoking neurally mediated syncope, induced hypotension in patients 1, 2, 4, and 5 and although a drug free tilt in patient 3 was normal, a modest dose of isoprenaline induced prolonged supine hypotension with exact reproduction of the patient's symptoms.<sup>13,14</sup> Adjuvant isoprenaline has been widely used to improve the sensitivity of tilt tests in the provocation of symptoms in patients with unexplained syncope.<sup>15</sup> The haemodynamic abnormalities and the response to orthostatic stress suggest that the mechanism of syncope is primarily vasodilatation, similar to a classical tilt induced vasovagal response.<sup>16,17</sup> Stimulation of ventricular mechanoreceptors leading to increased neural firing in unmyelinated C fibres to the brain stem results in sympathetic withdrawal and increased vagal tone; the primary features of the vasovagal reaction.<sup>18,19</sup> The absence of bradycardia at the time of maximal hypotension is unexplained but vasodepressor syncope (heart rate >60 beats/min) is not uncommonly seen in patients with tilt induced neurally mediated syncope.<sup>14</sup> It may be related to prevailing overall sympathovagal balance at the time of syncope.

The abnormal response to isoprenaline seen in patient 3 such that prolonged profound hypotension developed in the supine position is analogous to that seen in two reported cases in whom isoprenaline induced asystole or profound bradycardia.<sup>20,21</sup> This dramatic response to  $\beta$  adrenergic stimulation

is further evidence to support the concept that his symptoms were due to a mechanoreceptor mediated vasovagal type reaction.

The poor reproducibility of exercise induced hypotension in patients 2 and 3 suggests that it is important to perform repeated exercise tests in patients presenting with exercise induced syncope or presyncope if initial tests show an apparently normal haemodynamic response. Although only patient 4 had symptoms at times when she was not exercising, all five patients showed abnormal responses to a tilt test, which would seem to be a useful investigation in patients with exercise induced symptoms.<sup>4</sup> If as suspected, ventricular mechanoreceptor stimulation is responsible for triggering hypotension,  $\beta$  blockade is logical treatment as it attenuates cardiopulmonary receptor activity and is of value in some patients with tilt induced syncope.<sup>22 23</sup> Certainly metoprolol treatment has ameliorated the symptoms in patients 2 and 3 but was ineffective in patients 1 and 4, who responded to disopyramide another agent of documented efficacy in preventing tilt induced hypotension or bradycardia.<sup>24</sup> The rationale for the efficacy of disopyramide is based on its anticholinergic action, its mild peripheral vasoconstrictor, and negative inotropic effects.

In conclusion, exercise induced vasodepressor syncope may occur in patients without appreciable structural cardiac abnormalities and is caused by inappropriate vasodilatation probably triggered by stimulation of ventricular mechanoreceptors.

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