

# Increased orthostatic tolerance following moderate exercise training in patients with unexplained syncope

B L Mtinangi, R Hainsworth

## Abstract

**Objective**—To determine whether a programme of simple, moderate exercise training increases blood volume and improves orthostatic tolerance in patients with attacks of syncope or near syncope related to orthostatic stress.

**Design**—An open study in 14 patients referred with unexplained attacks of syncope, who were shown to have a low tolerance to an orthostatic stress test. Measurements were made of plasma and blood volumes, orthostatic tolerance to a test of combined head up tilt and lower body suction, and baroreceptor sensitivity by applying subatmospheric pressures to a chamber over the neck. Cardiorespiratory fitness was assessed from the relation between heart rate and oxygen uptake during a graded treadmill exercise test. Assessments were made before and after undertaking an exercise training programme (Canadian Air Force 5BX/XBX). **Results**—After the training period, 12 of the 14 patients showed evidence of improved cardiorespiratory fitness. All 12 patients were symptomatically improved; they showed increases in plasma and blood volumes and in orthostatic tolerance, and decreases in baroreceptor sensitivity. Despite the improved orthostatic tolerance, values of blood pressure both while supine and initially following tilting were lower than before training.

**Conclusions**—Exercise training has a role in the management of patients with syncope and poor orthostatic tolerance. It improves symptoms and increases orthostatic tolerance without increasing resting blood pressure.

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Keywords: orthostasis; syncope; baroreceptors; exercise

Syncope remains a significant diagnostic and therapeutic problem. Using tilt table testing, some patients prone to syncope have been shown to have a poor tolerance to orthostatic stress.<sup>1</sup> Simple tilt testing, however, often fails to make a diagnosis even in patients with histories strongly suggestive of posturally related syncope<sup>2</sup> and some other adjunct is needed to increase the stress. Many investigators have used isoprenaline, which certainly greatly increases the sensitivity of the test but also drastically reduces its specificity.<sup>3</sup> We employ a physiological rather than a pharmacological

approach to increasing orthostatic stress, by combining head up tilting with progressive lower body suction.<sup>4</sup> This test is not only repeatable in individual subjects but is also able to distinguish between patients with histories of orthostatic intolerance and asymptomatic control subjects.<sup>5</sup>

Using our new orthostatic stress test, we have been able to examine some of the predisposing influences leading to orthostatic intolerance and the effects of interventions which might lead to improvement. We have already examined the possible benefit of cardiac pacemakers and showed that orthostatic tolerance, assessed in this way, was the same irrespective of whether pacemakers were functioning or were programmed not to stimulate.<sup>6</sup> We also showed in both patients and volunteer subjects that orthostatic tolerance was highly significantly correlated with plasma and blood volume.<sup>7</sup> This led to the logical therapeutic strategy of trying to increase plasma volume. One way in which this was attempted was by salt loading, and in a double blind controlled trial salt loading usually increased both plasma volume and tolerance to orthostatic stress.<sup>8</sup> Salt loading, however, is not invariably successful. It has little effect in patients already consuming a large dietary salt intake. It may also be considered undesirable in older or hypertensive subjects because of the possible relations between stroke, hypertension, and salt intake.<sup>9</sup>

Physical exercise training is another procedure that has been shown to increase plasma and blood volumes.<sup>10</sup> However, its effect on orthostatic tolerance is uncertain.<sup>11-14</sup> Earlier conflicting reports may be explained by different intensities of training programmes and different methods for assessment of orthostatic tolerance. We therefore recently investigated the effects of a moderate training regimen (Royal Canadian Air Force 5BX/XBX) on asymptomatic subjects and showed that training did increase both plasma volume and orthostatic tolerance.<sup>15</sup> We therefore considered that it was safe to assess the same training regimen in patients who had been shown to have a low tolerance to orthostatic stress.

## Methods

### PATIENTS

Studies were carried out on 14 patients (six female, eight male) who had been referred for investigation because of unexplained attacks of syncope or near syncope. The mean age of the patients was 38 years (range 15 to 59) and their mean weight was 73 kg (50 to 105). Before

Institute for  
Cardiovascular  
Research, University  
of Leeds, Leeds  
LS2 9JT, UK  
B L Mtinangi  
R Hainsworth

Correspondence to:  
Dr Hainsworth.

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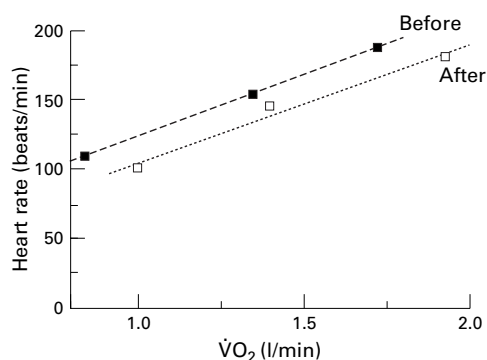


Figure 1 Relations between heart rate and oxygen consumption during exercise in one of the patients before and after undertaking the training programme. The lines are the linear regression and show the lower heart rates after training, at corresponding levels of oxygen consumption.

these studies all patients had resting ECG, 24 or 72 hour Holter monitoring, exercise ECG tests, and echocardiography, all with negative results. Four of the patients had had intracardiac electrophysiological studies and coronary angiography, and two had had EEG and computed tomography of the head, again with negative results. None of these patients had hypersensitive responses to carotid sinus massage. The frequency of attacks of syncope ranged from several times a week to one every several months, the median interval being three months. The duration of the problem ranged from two months to 10 years, median 12 months.

Before any investigations, potential subjects were asked to fast, to drink only water from midnight, and to report to the laboratory at 9.00 am. All subjects were informed of the nature of the study, which was approved by the ethics committee of the United Leeds Teaching Hospitals, and they gave their written consent.

#### ASSESSMENTS

The following procedures were carried out on each patient on two occasions, before and after undertaking an exercise training programme. A minimum interval of one hour was allowed between each test.

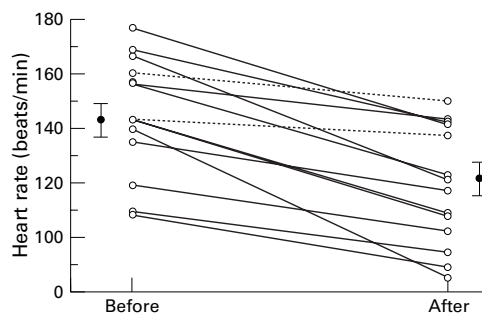


Figure 2 Values of heart rate taken from the regression lines (for example, fig 1) at values of oxygen consumption ( $\dot{V}O_2$ ) of 1.5 l/min. Points shown are values before and after training. Solid points with bars are the means with SE from all points. The dashed lines are the data from the two subjects in whom the change in the elevation of the regression line did not reach statistical significance. After training, all patients had lower values of heart rate at a  $\dot{V}O_2$  of 1.5 l/min.

#### Plasma volume determination

This was determined using the Evans blue dye dilution technique, as previously described.<sup>16</sup> Briefly, subjects initially rested supine for 30 minutes, after which a small catheter was inserted into an antecubital vein. After withdrawing blood for construction of a dye calibration line, a precisely weighed quantity of dye was injected and a clock started. Samples were withdrawn at five minute intervals from 10 to 35 minutes after injection, and plasma volume was calculated by reverse extrapolation of the log decay line back to the time of injection. The reproducibility of this technique had been shown to be  $\pm 45$  ml (2 SD).<sup>16</sup>

Blood volume was calculated from the plasma volume and packed cell volume. The repeatability of blood volume estimates is  $\pm 64$  ml.

#### Baroreceptor sensitivity

The ECG was recorded using chest wall leads, and a chamber constructed from a lightweight thermoplastic<sup>17</sup> was fitted round the neck. Pressure within the chamber was recorded using a pressure transducer (Gould-Statham P 23 Id, Oxnard, California, USA). Pressures of  $-0$ ,  $-20$ , and  $-40$  mm Hg were applied twice during held expiration and baroreceptor sensitivity determined from the slope of a linear regression relating pulse interval to neck chamber pressure.<sup>7,8</sup>

#### Orthostatic tolerance

The method involves a combination of head up tilting and lower body suction, and has been described in detail elsewhere.<sup>4,7,8</sup> Briefly, heart rate was determined from an ECG, while intermittent blood pressure recordings were made from an automatic sphygmomanometer (Infrasonde, Puritan-Bennett) and continuously from a finger monitor (Finapres, Ohmeda, Wisconsin, USA). Patients rested supine for 20 minutes, after which the following stresses were continued until the onset of presyncope: head up tilt by  $60^\circ$  for 20 minutes; then, while still tilted, lower body suction was applied at  $-20$  and  $-40$  mm Hg for 10 minutes each. The time of onset of presyncope, which was the measure of orthostatic tolerance, was the stage at which systolic pressure, recorded by Finapres, decreased below 80 mm Hg and continued to fall, and was accompanied by symptoms (dizziness, lightheadedness, or visual disturbances).

#### Exercise test

We used a submaximal exercise test and related steady state heart rate to oxygen uptake.<sup>18</sup> Chest wall ECG leads were fitted for determination of heart rate. Expired gas was collected in a 120 litre spirometer using a two way respiratory valve. Oxygen and carbon dioxide contents were determined using a Servomex OA 540 paramagnetic analyser (Taylor Analyticals) and a Binos-1 infrared analyser (Leybold-Heraeus, Köln, Germany). Subjects exercised using the standard Bruce protocol,<sup>19</sup> expired gas being collected for the last minute of each three minute stage.

Table 1 Effects of training on plasma and blood volumes, orthostatic tolerance, and baroreceptor sensitivity.

	Study 1	Study 2	Difference	p Value
Body weight (kg)	73.2 (4.2)	72.6 (4.1)	-0.6 (0.3)	NS
Plasma volume (ml)	3155 (222)	3317 (225)	+162 (19)	0.0001
Plasma volume (ml/kg)	43.2 (2.3)	46.1 (2.5)	+2.9 (0.3)	0.0001
Blood volume (ml)	4930 (337)	5137 (340)	+208 (25)	0.0001
Blood volume (ml/kg)	67.5 (3.4)	71.4 (3.6)	+3.9 (0.4)	0.0001
Packed cell volume (%)	36.1 (0.6)	35.4 (0.6)	-0.7 (0.2)	NS
Time to syncope (min)	23.5 (2.7)	28.6 (1.4)	+5.1 (0.9)	0.0001
Baroreceptor sensitivity (ms/mmHg)	5.3 (0.5)	3.6 (0.5)	-1.7 (0.2)	0.01

Values shown are means (SEM) from 14 patients before and after training programme. Significance of changes was assessed using *t* test for paired data.

Table 2 Effects of training programme on supine and tilted values of heart rate and blood pressure

	Study 1	Study 2	Difference	p Value
Supine heart rate (beats/min)	71.4 (2.5)	64.7 (2.2)	-6.6 (0.5)	0.0001
Tilted heart rate (beats/min)	91.9 (3.7)	86.0 (3.3)	-5.9 (0.5)	0.0001
Supine systolic pressure (mm Hg)	109 (1.8)	104 (1.6)	-5.1 (0.4)	0.0001
Tilted systolic pressure (mm Hg)	111 (2.1)	110 (2.0)	-1.2 (1.1)	NS
Supine diastolic pressure (mm Hg)	62 (1.8)	56 (1.4)	-6.0 (0.6)	0.0001
Tilted diastolic pressure (mm Hg)	76 (1.4)	71 (1.1)	-5.8 (0.4)	0.0001

Values are mean (SEM) from 14 patients, before and after the training programme. Significance of changes was assessed using the *t* test for paired data.

Values of heart rate were plotted against oxygen consumption ( $\dot{V}O_2$ ) using data from each stage of exercise and a least squares regression analysis performed between heart rate and oxygen uptake. From the regression equation we determined heart rate at  $\dot{V}O_2$  of 1.5 l/min<sup>20</sup> and compared repeated estimates by determining whether there was a significant shift in the elevation of the regression lines.<sup>21</sup>

#### TRAINING PROTOCOL

We used the 5BX programme for men and the XBX for women developed by the Royal Canadian Air Force.<sup>22</sup> This is a gently progressive regimen of strengthening and endurance training occupying about 11–12 minutes a day and aiming for an age related “target.” This

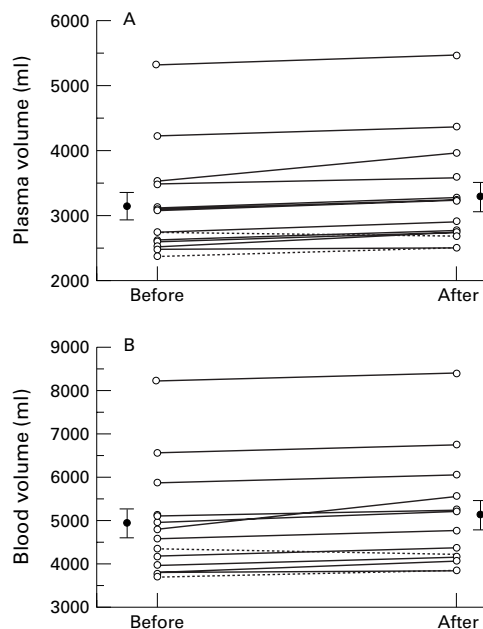


Figure 3 Values of plasma volume before and after training. Points joined by dashed lines are from patients who failed to show a significant change in the slope of the heart rate to  $\dot{V}O_2$  relation.

programme requires no special equipment and is considered to be safe, having been used in studies of patients with cardiac<sup>23</sup> and pulmonary disorders.<sup>24</sup>

After the initial assessment and after the protocol had been explained to the patients, they were requested to contact one of the investigators when they had either reached their target or had progressed as far as they felt able.

#### Results

All patients were able to undertake the training programme and none reported any particular difficulties including injuries or muscle strains.

#### SUBMAXIMAL EXERCISE TEST

Figure 1 shows the relation between heart rate and oxygen consumption in one patient before and after training. Analyses of similar pairs of plots determined from all 14 patients revealed that following training all the plots were depressed. The interpolated values of heart rate at  $\dot{V}O_2$  1.5 l/min were lower in all patients following training (fig 2). However, analysis of the elevation of the lines revealed significant changes (*p* between 0.05 and 0.001) in 12 of the patients. Those failing to show significant changes are shown as dashed lines in the figures. These patients admitted to having undertaken the training programme only intermittently.

#### PLASMA AND BLOOD VOLUMES

Overall there were significant increases in plasma and blood volumes (*p* < 0.0001) with no change in packed cell volume (table 1). Of the 14 patients studied, plasma and blood volumes increased beyond the 95% tolerance limits of the method in 12. The two patients who failed to show significant changes in the heart rate to  $\dot{V}O_2$  relation also did not show significant changes in plasma and blood volumes (fig 3).

#### BLOOD PRESSURES, ORTHOSTATIC TOLERANCE, AND BARORECEPTOR SENSITIVITY

Values of heart rate and systolic and diastolic blood pressures in the supine position were significantly lower after training (table 2). Heart rate and diastolic pressure (averages from readings taken at between two and six minutes of head up tilt) were also significantly decreased. These times of measurement were before the onset of presyncope in all the patients.

Orthostatic tolerance increased significantly overall (table 1) and individually in all except the two who failed to show a training effect (fig 4). Orthostatic tolerance increased by three minutes or more in all patients who showed increases in plasma volume of 150 ml or more (fig 5).

Baroreceptor sensitivity decreased following training in all subjects. However, in one of the patients who failed to show a training effect on the heart rate/ $\dot{V}O_2$  slope, baroreceptor sensitivity did not change outside the 95% tolerance limits of the measurement (fig 6).

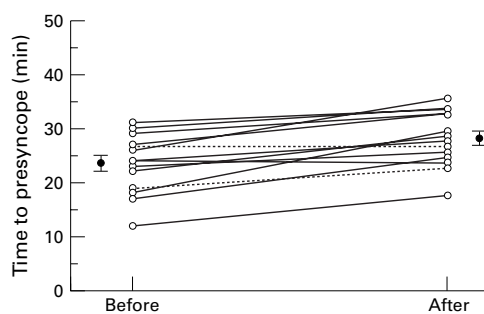


Figure 4 Values of orthostatic tolerance (time to presyncope) in patients before and after training. The stages of the test were: 0–20 minutes, head up tilt; 20–30 minutes, tilt and lower body suction at  $-20$  mm Hg; after 30 minutes, tilt and lower body suction at  $-40$  mm Hg. Dashed lines are from patients failing to show significant change in heart rate to  $\dot{V}O_2$  relation. All other patients showed increased tolerance, with eight changing up to the next stress level.

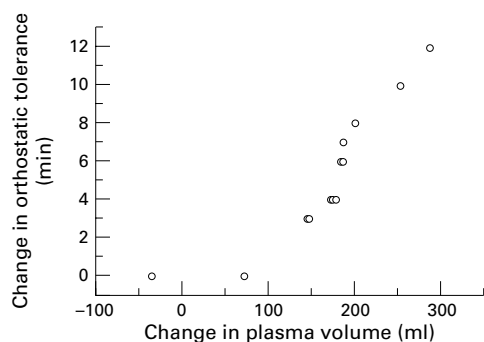


Figure 5 Relation between change in orthostatic tolerance and change in plasma volume. Note that all patients who showed increases in plasma volume of 150 ml or more showed increases in orthostatic tolerance.

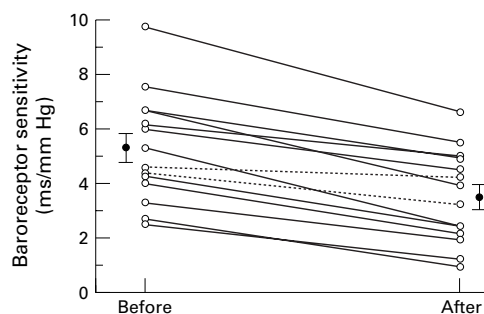


Figure 6 Effects of training on baroreceptor sensitivity. Baroreceptor sensitivity decreased in all patients, although in one of those who did not show a significant change in the heart rate/ $\dot{V}O_2$  slope, baroreceptor sensitivity did not change outside the error of the method.

#### SYMPTOM CHANGES

All patients except the two who failed to show a significant training effect claimed to feel better. None of the others had experienced any attacks of syncope since starting the programme and all indicated their intention to continue regular exercise.

#### Discussion

Patients with unexplained attacks of posturally related syncope have been particularly difficult to manage. Diagnosis is difficult and unless positive results can be obtained by tilt table tests, it is often made simply by exclusion of other causes. Various pharmacological agents such as  $\beta$  adrenoreceptor blocking drugs may

be helpful,<sup>25, 26</sup> but in some patients they may exacerbate the problems.<sup>27</sup> Pacemaker implantation has often been used, but some studies have found little or no benefit.<sup>6, 28</sup> Vasoconstrictors may be helpful but are not without problems.<sup>29</sup>

We had previously noted that a person's tolerance to an orthostatic stress was correlated with plasma volume, and we reported results of a trial which showed that when plasma volume was expanded by increasing the dietary salt intake, orthostatic tolerance increased and symptoms improved. We stated that salt loading could have an important role in the management of patients with orthostatically related syncope. However, salt is not the complete answer. First, it is not effective in about one third of patients, particularly those already consuming large quantities of salt.<sup>8</sup> Second, salt may be considered to be undesirable in some people, because of coexisting cardiac conditions or because of the association with hypertension.<sup>9</sup>

Exercise training is widely regarded as being of benefit to health and, if it can also be shown to benefit people with posturally related syncope, it be recommended as a desirable form of treatment. We were initially concerned that training might have adverse effects in some people, as there have been reports indicating that highly trained athletes could have poor tolerance to orthostatic stress. Indeed, one went so far as to state that "trained men can run but cannot stand."<sup>11</sup> For this reason we carried out an earlier study of the effects on healthy volunteers of the training programme selected for our patients.<sup>15</sup> This study showed that it was of benefit to subjects with average and below average orthostatic tolerance and therefore was unlikely to cause adverse effects in any of our patients.

The results of our present study confirmed that exercise training improved orthostatic tolerance, and this was associated with increases in plasma and blood volumes and decreases in baroreceptor sensitivity. Of the 14 patients studied, the only two who did not benefit from training were those who showed minimal other evidence of training, and it was apparent that they had not regularly undertaken the schedule.

We recognise that there are limitations to our study. With a programme of this sort it is clearly impossible to devise a double blind controlled trial. We also did not include a control group as such. However, we have previous data where similar measurements were carried out. One example was the earlier salt study,<sup>8</sup> where in the placebo group there were no significant effects on any of the variables measured in the present study. The two patients who failed to show significant cardio-respiratory evidence of training in a sense provided some control against which to compare the others.

We feel that exercise training has a place in the management of patients with orthostatic syncope. Symptoms were improved and all patients were free from syncope after undertaking the programme. All indicated their

intention to continue with the exercises. Training does, however, require motivation on the part of the patients. Also not all people are able to undertake the programme. In particular various orthopaedic conditions or other coexisting medical problems preclude effective training. However, for those patients willing and able to exercise there are undoubted health benefits. One benefit may be that, although training enables people to withstand an orthostatic stress better, it nevertheless resulted in a decrease in resting blood pressure. In this respect it may have an advantage over salt which is likely to increase the blood pressure.

We suggest that both salt loading and exercise training can be useful in the management of patients with poor orthostatic tolerance. Exercise training would be particularly recommended in unfit people who are able to exercise and in those for whom salt loading might be considered inappropriate.

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