Exercise-related syncope in young competitive athletes without evidence of structural heart disease

Clinical presentation and long-term outcome

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Aims Exercise-related syncopal spells in athletes receive great attention and are a source of anxiety in the sporting world. The aim of the present study is to describe the clinical presentation, the yield of the initial diagnostic work-up and the long-term outcome of a series of consecutive competitive athletes with recurrent exercise-related syncopal spells.

Methods and Results The study cohort included 33 athletes (20 females, mean age 21.4 ± 3.2 years) referred for recurrent unexplained episodes of exercise-related syncope (mean number of spells before evaluation 4.66 ± 1.97). All athletes underwent an extensive evaluation, including echocardiography, 24-h electrocardiographic monitoring, exercise testing, cardiac electrophysiological study and head-up tilt testing. The echocardiographic examination revealed the presence of a mitral valve prolapse in two cases (6.0%). During maximal exercise testing, four athletes (12.1%) developed hypotension associated with presyncope. Twenty-two subjects (66.6%) showed a positive response to head-up tilt testing. During follow-up (33.5 ± 17.2 months) 11/33 athletes (33.3%) showed at least one recurrence of exercise-related syncope (mean time to first recurrence 20.4 ± 14.5 months). No other adverse event of any kind was noted during follow-up. The Kaplan–Meier estimates of first recurrence of exercise-related syncope after 12, 36 and 60 months were 9.1%, 24.4% and 42.9%. The number and frequency of exercise-related syncopal spells before evaluation were found to be univariate predictors of syncope recurrence (P<0.001). However, in the multivariate analysis, the number of exercise-related syncopal spells before evaluation was found to be the only independent predictor of syncope recurrence (P<0.05).

Conclusions These findings support the idea that recurrent exercise-related syncope is not associated with an adverse outcome in athletes without cardiac disease.

Key Words: Syncope, exercise, athletes.

See doi:10.1053/euhj.2001.3123 for the Editorial comment on this article

Introduction

Young competitive athletes are usually considered the healthiest component of our society[1]. Consequently, the occurrence of any kind of adverse clinical event on the athletic field has a significant impact on the lay and medical community[2]. In particular, exercise-related syncopal spells in young athletes receive great attention and cause upset in the sporting world[3,4]. In addition, owing to the possible life-threatening causes of such a condition, athletes with syncope are barred from further participation in competitive sport activity, until a clear explanation for their episodes is found[5,6]. Cardiac disorders, such as hypertrophic cardiomyopathy, right ventricular dysplasia, anomalous coronary artery origin, myocarditis and long QT syndrome, should be carefully excluded by appropriate diagnostic work-up in all cases[3–6]. However, when no clinical or laboratory evidence of structural heart disease is found, an exercise-related neurocardiogenic reflex may be the cause of recurrent unexplained syncopal episodes in athletes[7–11]. The aim of the present paper is to describe the clinical presentation, the yield of the initial diagnostic work-up and the subsequent long-term outcome of a series of consecutive young competitive athletes referred for recurrent unexplained exercise-related syncopal spells.
Patients and methods

Study population

The study cohort included 33 consecutive young competitive athletes (20 females and 13 males, with a mean age of 21.4 ± 3.2 years; 10 runners, seven basketball players, six soccer players, five volleyball players, four cyclists, one triathlete) referred to the Syncope Clinic of our institution between April 1994 and February 2000, with recurrent unexplained episodes of exercise-related syncopal spells. All subjects included in the study were highly trained athletes, competing at a national (27 athletes) and international level (six athletes), who had had at least two witnessed episodes of syncope during or immediately after a period of exercise in the preceding 6 months. Syncope was defined as a sudden transient loss of consciousness with inability to maintain postural tone and with spontaneous recovery.

A thorough description of syncopal spells was obtained in all cases. Moreover, all available witnesses (parents, other athletes, trainers) were interviewed, in order to collect all possible information about the specific circumstances and the athlete’s appearance and behaviour during the episodes. As syncope presenting during exercise tends to be more frequently associated with structural heart disease and with an unfavourable outcome, specific care was taken to distinguish syncopal spells occurring during exertion from those taking place in the post-exertional state. Only syncopal spells presenting during continuous effort and causing sudden unintentional interruption of the activity, together with falling, were considered to have occurred during exercise.

No subjects were receiving medication of any kind, and all denied the consumption of illegal or recreational drugs.

Preliminary work-up

Before referral, all athletes were submitted to a preliminary non-invasive evaluation including history, physical examination, full routine laboratory testing, 12-lead electrocardiography and Doppler-echocardiography. No major cardiac, metabolic or neurological abnormality was revealed. Subsequently, at the Syncope Clinic of our institution, all referred athletes underwent further extensive clinical and laboratory evaluation, including 24-h electrocardiographic monitoring, exercise tolerance testing (Bruce protocol), electroencephalography, CT scanning of the central nervous system and cardiac electrophysiological study.

Head-up tilt testing

After the above reported preliminary diagnostic work-up, all subjects underwent head-up tilt testing, according to a previously described protocol. The test was performed in the morning, in a fasting state. An electronically controlled tilt table with a foot-board for weight-bearing and restraining belts was used for the procedure. Continuous electrocardiographic monitoring for heart rate and rhythm was performed, while blood pressure was non-invasively measured beat to beat by means of an Ohmeda Finapress 2300 photoplethysmographic device (Louisville, Colorado, U.S.A.). Subjects were initially tilted at 60° for 30 min (control phase). Subsequently, if no symptoms occurred, participants received 1.25 mg of isosorbide dinitrate sublingually and continued to be tilted for additional 15 min (pharmacological phase). The completion of the two stages without symptoms indicated a negative test. The test was considered positive if syncope occurred in association with hypotension and/or bradycardia. If syncope did occur, the procedure was terminated by rapidly lowering the tilt table to the horizontal position. In accordance with previous reports and for the purpose of the study, two main forms of positive response to tilt table test were identified: (1) a vasodepressor form (syncpe associated with a systolic blood pressure decrease to 60 mmHg or less, but without significant heart rate reduction); (2) a cardioinhibitory form (syncpe associated with a systolic blood pressure decrease to 60 mmHg or less and heart rate reduction to less than 40 beats. min⁻¹).

Clinical management and follow-up

After completion of the diagnostic evaluation, all athletes underwent counselling regarding the possible diagnosis and probable pathophysiology of their syncopal spells. All subjects were reassured and counselled to recognize their pre-syncopal prodromes, and urged to take appropriate postural manoeuvres when presyncope, in order to avoid traumatic injuries. No specific pharmacological treatment was started. All subjects were asked to immediately notify any syncope recurrence. A clinical follow-up, including physical examination and a 12-lead electrocardiogram, was programmed on a 6-monthly basis. All athletes underwent a complete pre-participation screening every year following the initial work-up, as required by the Italian legislation for qualification in competitive sports. For these athletes, such an evaluation was planned to include a physical examination, 12-lead electrocardiography, exercise tolerance testing, 24-h electrocardiographic monitoring and Doppler-echocardiography.

Statistical analysis

Mean (± standard deviation) and median values were calculated for continuous variables, while frequencies were measured for categorical variables. Differences between groups were analysed by unpaired Student’s
t-test for continuous variables and by chi-square or Fisher’s exact test for categorical variables as appropriate.

The cumulative risk of recurrence of syncope was estimated by means of the Kaplan–Meier method. Survival curves of subgroups were than formally compared using the log-rank test. The Cox proportional hazards regression method was used to determine the relationship of baseline characteristics to syncope recurrence during follow-up. The following variables, determined from the baseline evaluation, were considered potential predictors of syncope recurrence: age, gender, number and frequency of exercise-related syncopal spells in clinical history and tilt test results. These variables were then analysed in a stepwise fashion to develop Cox models of the study end-point (recurrence of exercise-related syncope).

Data analysis was performed using the SPSS statistical software package (SPSS 8.0, Chicago, Illinois). A P value <0·05 was considered statistically significant.

**Results**

**Syncope history**

In the study population, the mean number of exercise-related syncopal spells before evaluation was 4·66 ± 1·95 (median four episodes), with an estimated frequency of 0·29 ± 0·07 spells/month (median 0·28 spells/month). In 20 (60·7%) athletes, syncope occurred only in association with exercise, while 13 subjects (39·3%) had also shown syncopal episodes during ordinary daily activities (2·31 ± 1·91, median two episodes). Syncope occurred during exercise in seven cases (21·2%; three runners, two soccer players, one basketball player and one volleyball player), immediately after cessation of exercise in 16 cases (48·4%; five basketball players, four cyclists, three soccer players, two runners, two volleyball players) and both during and after exercise in 10 cases (30·4%; five runners, two volleyball players, one basketball player, one soccer player and one triathlete). Overall, 17 athletes (51·5%) reported at least one syncopal episode during exercise; these events were found to be almost invariably associated with running (16/17 cases, 94·1%). Prodromal symptoms (nausea, diaphoresis, lightheadedness, palpitations, epigastric discomfort) preceding syncope were reported by 23 athletes (69·6%). Mild residual symptoms after recovery of consciousness were reported in all cases, with fatigue being the most common complaint (22 cases, 66·6%). Urinary incontinence was not noted in any case. Syncopal episodes were followed by minor traumatic injuries in 16 athletes (48·4%). All of these syncope-related traumatic lesions were associated with syncopal spells occurring during exercise.

**Preliminary diagnostic work-up**

The echocardiographic examination revealed the presence of a mitral valve prolapse with mild regurgitation in two cases (6·0%). During maximal exercise testing, four athletes (12·1%) developed hypotension associated with lightheadedness or pre-syncope immediately after peak exercise; such haemodynamic impairment resolved in all cases between the second and the fifth minute of the recovery phase with assumption of the supine position and elevation of both legs. During these exercise-related episodes of hypotension, electrocardiographic monitoring indicated the presence of sinus tachycardia in all cases. All of these four athletes (two runners, one soccer player and one basketball player) had reported syncopal episodes during exercise.

No other significant abnormality was noted during the preliminary clinical and laboratory assessment.

**Head-up tilt testing**

Twenty-two subjects (66·6%) showed a positive response to head-up tilt testing. In 14/22 cases (63·6%) the test was found to be positive in the initial unmedicated control phase of the test, while in the remaining 8/22 (36·4%) athletes the test was positive after pharmacological provocation with sublingual isosorbide dinitrate. In 10/22 cases (45·4%) tilt-induced syncope was associated with an asystolic pause of more than 3 s with sinus arrest (cardioinhibitory response with a mean duration of asystole of 9·8 ± 6·3 s).

Three of the four athletes with hypotension in the course of the exercise test had a positive response to head-up tilt testing.

**Outcome events**

All of the athletes continued their training and competitions after the initial diagnostic evaluation, and were followed for a mean period of 33·5 ± 17·2 months. During the follow-up period, 11/33 athletes (33·3%) had at least one recurrence of exercise-related syncope (mean time to first recurrence of syncope 20·4 ± 14·5 months; median time to first recurrence of syncope 14 months). Two athletes had a second recurrence in one case after 7 months and in the other after 9 months from the first episode. In three athletes the recurrence of syncope was associated with minor syncope-related traumatic injuries. No other adverse event of any kind was noted during follow-up. Moreover, the scheduled yearly cardiovascular evaluation revealed no significant abnormality in any subject.

The Kaplan–Meier actuarial estimates of a first recurrence of exercise-related syncope after 12, 36, and 60 months were 9·1%, 24·4%, and 42·9%, as shown in Fig. 1. The differences between the athletes with recurrence of syncope during follow-up and the rest of the study population are shown in Table 1. Both the number and the frequency of exercise-related syncopal spells before evaluation were found to be univariate predictors of syncope recurrence during follow-up (P<0·001 for
both). However, in the multivariate Cox proportional hazards analysis, the number of exercise-related syncopal spells before evaluation was found to be the only independent predictor of syncope recurrence during follow-up (risk ratio 1.29; 95% confidence interval 1.01–1.65; \( P = 0.0383 \)). In particular, athletes with up to three episodes of exercise-related syncope in the clinical history showed no evidence of recurrence of syncope for more than 3 years (Fig. 2).

**Discussion**

This clinical investigation describes the presenting features and the long-term outcome of a series of young competitive athletes with recurrent unexplained episodes of exercise-related syncope. In all cases the presence of structural heart disease was excluded by thorough cardiovascular evaluation, which included conventional non-invasive diagnostic procedures (echocardiography, Holter monitoring and exercise testing), followed by electrophysiological study. The diagnostic work-up was then completed by head-up tilt testing, which was effective in reproducing a syncopal spell in about 65% of cases. Such findings are in accordance with previous studies, suggesting that most of the reported episodes of exercise-related syncope in competitive athletes may be related to a neurocardiogenic reflex\[7–11\]. In fact, such a disorder of autonomic cardiovascular regulation may suddenly develop during strenuous effort and eventually lead to loss of consciousness, as some authors have previously reported\[9,10\] and were directly observed during exercise testing in 12.1% of the athletes of our series.

The outcome of this specific population of athletes with recurrent exercise-related syncope, but without any clinical or laboratory evidence of cardiac disease, has been assessed in a follow-up lasting up to 68 months. During such a period of observation the athletes neither interrupted their training and competitions, nor underwent any specific therapeutic intervention, with the exception of reassurance and counselling. During follow-up, exercise-related syncope recurred in a relevant percentage of athletes, with an estimated incidence of about 10% per year. However, the risk of recurrence of syncope after the initial diagnostic work-up could not be predicted by any specific laboratory finding, including tilt test outcome. Only the absolute number of exercise-related syncopal spells before the baseline diagnostic

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**Figure 1** Kaplan–Meier actuarial estimates of a first recurrence of exercise-related syncope in the whole study population.

**Table 1** Characteristics of athletes grouped according to clinical outcome

<table>
<thead>
<tr>
<th></th>
<th>Recurrence of syncope</th>
<th>No recurrence of syncope</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of athletes</td>
<td>11</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Males/Females</td>
<td>5/6</td>
<td>8/14</td>
<td>ns</td>
</tr>
<tr>
<td>Age (years)</td>
<td>21.7 ± 3.0</td>
<td>21.2 ± 3.4</td>
<td></td>
</tr>
<tr>
<td>Exercise-related syncopal episodes before evaluation (number)</td>
<td>6.5 ± 1.6</td>
<td>3.7 ± 1.3</td>
<td>( P &lt; 0.001 )</td>
</tr>
<tr>
<td>Frequency of exercise-related syncope before evaluation (spells/month)</td>
<td>0.35 ± 0.08</td>
<td>0.26 ± 0.05</td>
<td>( P &lt; 0.001 )</td>
</tr>
<tr>
<td>Syncope immediately after exercise (number and percentage)</td>
<td>2 (18.2%)</td>
<td>5 (22.7%)</td>
<td>ns</td>
</tr>
<tr>
<td>Syncope during and after exercise (number and percentage)</td>
<td>4 (36.3%)</td>
<td>12 (54.6%)</td>
<td>ns</td>
</tr>
<tr>
<td>Positive response to tilt testing (number and percentage)</td>
<td>8 (72.7%)</td>
<td>14 (63.6%)</td>
<td>ns</td>
</tr>
</tbody>
</table>

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Eur Heart J, Vol. 23, issue 14, July 2002
evaluation was found to be an independent predictor of recurrence of exercise-related syncope. These findings are consistent with previous studies which have shown that in patients with known or suspected neurally mediated syncope the risk of syncope recurrence can be better predicted by clinical history than by laboratory testing[17]. Overall, the results of the initial diagnostic work-up, as well as the directly observed long-term outcome, support the idea that all of our athletes had a neurally mediated form of exercise-related syncope.

Competitive athletes presenting with a history of unexplained exercise-related syncope require an accurate and effective clinical assessment. In fact, syncopal spells occurring either during or immediately after a period of exercise, should always be considered as a possible sign of potentially lethal cardiac problems until otherwise proven[3,4]. Consequently, the diagnostic work-up should be aimed at excluding the presence of any significant underlying structural heart disease[3,4]. In particular, the cardiovascular evaluation should always begin with echocardiography, followed by exercise stress testing and Holter monitoring[3,4]. If no evidence of organic cardiac disease is demonstrated by such methods, further diagnostic assessment should include head-up tilt testing as recommended in a recent ACC guideline statement (class I indication)[18]. Such methodology may be helpful by providing evidence of the possible neurocardiogenic nature of the episodes of exercise-related loss of consciousness, while also allowing detailed observations on the pathophysiological events taking place in the course of a syncopal spell[11,18]. However, in pursuing such a diagnostic approach the clinician should be aware that the sensitivity and the specificity of head-up tilt testing in the specific subset of trained athletes is currently unknown[11]. If the non-invasive cardiovascular evaluation does not provide any significant result, an electrophysiological study may be considered (class II indication according to the ACC/AHA guidelines)[19]. An invasive approach has been advised by some authors[20], who reported that tachyarrhythmias might represent an underlying cause of syncope in some athletes, even in the absence of any detectable structural heart disease. The actual yield of such invasive methodology in the specific subset of athletes with syncope and no evidence of heart disease is currently unknown[4].

In conclusion, this study provides evidence that exercise-related syncope is not associated with adverse outcomes in competitive athletes with a fully negative cardiovascular work-up. Accordingly, if a cardiac disease is excluded by appropriate diagnostic assessment the athlete with exercise-related syncope should not be barred from participation in athletics. However, correct and exhaustive instructions should be given to the athlete in order to reduce the hazards of possible syncope-related traumatic injuries.

References


