Long-term outcome of patients with asystole induced by head-up tilt test

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Aims To analyse the long-term outcome of the largest reported cohort of patients presenting asystole during head-up tilt test.

Methods and Results Since 1990, 1322 patients with syncope of unknown origin have undergone tilt-table testing. Of those, 330 patients (24·9%) presented an abnormal response (syncope or pre-syncope). Furthermore, 58 of those patients (17·5%) suffered a period of asystole (≥3000 ms) during the test. Asystole (median (interquartile range)) lasted 10 (4, 19·2) s (range 3–90). Two different protocols (angles) of tilting (Westminster (60°) n=1124; isoproterenol (80°) n=198) influenced the time to the syncopal episode (13 (6·5, 20·5) vs 2 (1, 6·5) min, \( P=0·0005 \)) but not the duration of the asystole. During this period, therapy for asystole featured three different stages: first patients were treated with pacemakers; later drug therapy (metoprolol and/or etilefrine) was recommended; lastly (from 1995), no specific treatment was given. In a cohort age- and gender-matched study, those patients without were compared to those with asystole in a 2:1 basis. During 40·7 months of follow-up (17·7, 66·8), 12 patients (20·6%) with asystole had syncopal recurrences. Furthermore, 34 patients (28·8%) without asystole presented syncopal episodes during a follow-up of 51·6 months (29·3, 73·1) (\( P=\text{ns} \)). The Kaplan–Meier analysis in patients with and without asystole showed a mean time free of recurrence of 92·6 ± 6 months vs 82·6 ± 4·7 months (\( P=\text{ns} \)). The previous number of syncope had a significant relationship with recurrences (\( P=0·002 \)), but not therapy. There were no cardiac related deaths.

Conclusions (1) Asystole during head-up tilt test does not imply a malignant outcome and syncope recurrence is low; (2) pacemaker or drug therapy do not significantly influence outcome which correlates to the previous number of syncopal episodes but not to gender, age, asystole occurrence, asystole duration and timing to asystole during head-up tilt test; (3) tilting protocol (angle) might influence time to and incidence of asystole during head-up tilt test.


Key Words: Asystole, treatment, syncope, tilt-test.

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Introduction

Since Kenny et al.[1] suggested use of the tilt-table test as a screening strategy for neurocardiogenic syncope, various physiopathological responses[2,3] have been observed. At present, neurocardiogenic syncope is generally considered to be a benign condition[4], although some authors have related it to rare events of sudden death[5]. Among patients developing bradycardia during the head-up tilt test, there is a subgroup in whom an asystole occurs (Fig. 1) and on rare occasion has even required measures of cardiopulmonary resuscitation[6–8]. Few data on prognosis of those patients with asystole during head-up tilt test exist[9–12]. Therefore, the aim of this paper is to present the long-term outcome of the largest cohort of such patients.

Methods

Patients

From September 1990 to May 2000, 1322 patients with syncope of unknown origin were referred for head-up
tilt test at the Cardiology Department of ‘Virgen del Rocio’ General Hospital (Sevilla, Spain). All patients had suffered: (a) ≥2 syncopal episodes, (b) 1 syncopal and ≥2 pre-syncopal episodes, or (c) a single episode of syncope causing injury or hospital admission. All patients had normal ECG, echocardiogram, exercise test and Holter monitoring. After informed consent was obtained, all patients underwent head-up tilt test off drugs.

From those 1322 patients, an abnormal test response (syncope or pre-syncope with vasodepressor, cardio-inhibitory and mixed responses) was observed in 330 patients (24.9%), and 58 of those 330 patients (17.5%) suffered an asystole (pause ≥3000 ms) during head-up tilt test and form the cohort of the study (group A).

In order to compare the influence of the asystolic response during head-up tilt test on prognosis, a control group (group B) was composed of patients with a vasovagal response during head-up tilt test but without asystole. These patients were chosen at random, but on an age- and gender-matched 2:1 basis, bearing in mind the head-up tilt test protocol and time periods in which the various treatment strategies tended to be favoured (e.g. there would be 12 controls for the first six pacemaker-treated patients, etc.). The clinical characteristics of both groups were comparable (Table 1).

**Definitions**

Syncope was defined as sudden transient loss of consciousness, with inability to maintain postural tone, and with spontaneous recovery. Pre-syncope was defined as the complex of premonitory signs and symptoms of imminent syncope (e.g. severe light-headedness, severe weakness, transient graying of vision, or hearing loss) with difficulty in maintaining postural tone. A vasovagal or neurocardiogenic response to head-up tilt test was defined as reproduction of the spontaneous syncope or

**Table 1** Demographic characteristics of study (group A) and control (group B) populations. There was no significant difference between the groups

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=58)</th>
<th>Group B (n=118)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (%)</td>
<td>24 (41%)</td>
<td>57 (48%)</td>
</tr>
<tr>
<td>Age (year)</td>
<td>35 (19.5, 59.5)</td>
<td>29 (17, 51)</td>
</tr>
<tr>
<td>Number of syncopes</td>
<td>3 (1, 5)</td>
<td>3 (1, 8)</td>
</tr>
<tr>
<td>Evolution time (months)</td>
<td>24 (6, 60)</td>
<td>36 (3, 118)</td>
</tr>
<tr>
<td>Follow-up time (months)</td>
<td>40-7 (17-7, 66-8)</td>
<td>51-6 (29-3, 73-1)</td>
</tr>
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</table>

Data are expressed as median (interquartile range).
pre-syncpe in association with hypotension, bradycardia, or both (decrease in systolic blood pressure >50% and decrease in heart rate >30% of the maximal value observed in the upright position). Asystole was defined as an interruption in ventricular activity (during a cardioinhibitory or mixed response to head-up tilt test), lasting for 3000 ms or more based on the definitions of the VASIS study and ACC recommendations for pacing in bradyarrhythmias.

**Therapeutic strategies and follow-up**

The decision on how and who to treat was not based on the number of previous syncopes, but on our own chronological experience. From September 1990 to November 1992, permanent DDD-pacing was recommended to all patients with asystole (n=6) but one patient refused this treatment. From November 1992 to June 1995, drug therapy (metoprolol 50 mg . 12 h⁻¹; etilefrine 10 mg . 8 h⁻¹) or implanting a pacemaker, if drug therapy failed to prevent recurrences of syncope, was recommended to those (n=21) patients with asystole during head-up tilt test. At the time of writing, only nine of those patients are persisting with pharmacological treatment. Among these nine patients, one pacemaker has also been implanted. After June 1995, patients (n=31) received no specific treatment. However, if recurrence occurred, then drug or pacemaker therapy was considered.

As previously mentioned, group A and B patients were randomly matched on gender, age and treatment period. In group B, 11 first period patients had no treatment, and one received a pacemaker. Forty-two patients of the second period received pharmacological treatment. At the time of writing, only 14 patients are still being administered this therapy. Among these 14 patients, one pacemaker has also been implanted. In 64 patients of the third period, two are empirically treated, and one received a pacemaker.

All patients of both groups received advice, increased their salt intake, and were informed about how to avoid the classic situations which facilitate syncope. They were also informed on how to recognize syncope prodromes and were urged to sit down or lie down quickly. After discharge, follow-up at our outpatient clinic or by phone was carried out every 6–12 months.

**Statistical analysis**

In order to compare the influence of the asystolic response during head-up tilt test on prognosis, a cohort study was designed. Continuous variables were expressed as median (interquartile range) when their distribution is not normal, and as mean ± SD when their distribution is normal. These variables were compared by Mann–Whitney or Student t-test. The Fisher or chi-square test was used for comparison of qualitative variables. The cumulative risk of syncope over time was estimated using the Kaplan–Meier procedure, and Kruskal–Wallis test was used for correlation between treatment and time to recurrence. A two-tailed P value <0.05 was considered significant. Data were analysed with version 10 of SPSS software (SPSS, Chicago, Illinois).

Asystole occurred in 45 of 1124 patients (4%) and in 13 of 198 patients (6·5%) using a Westminster and isoproterenol protocol (tilting angle of 60° and 80°) (P<0·04), respectively. There were no differences in age [29 (17·5, 49) vs 30 (16, 52) years], gender (female: 40% vs 46%), number of previous syncopes [4 (2, 12) vs 3 (1·5, 8·5)] or duration of symptoms [42 (4·5, 129) vs 36 (6, 114) months] between patients with asystole included in both tilting protocols. Overall, the asystole lasted for a median of 10 (4, 19·2) s (range 3–90). This event occurred after 13 (6·5, 20·5) min and lasted for a median of 10 (4, 20) s (range 3–90) using the Westminster (tilting angle of 60°) protocol. However, using the isoproterenol protocol (tilting angle of 80°), the asystole occurred after 2 (1, 6·5) min of isoproterenol infusion (P=0·005 compared to Westminster protocol) and its mean duration was 13 (15, 7) s (range 3–36) (P=ns compared to Westminster protocol).

Follow-up was obtained from all patients. There were no cardiac-related deaths (mean follow-up 43·4 months (18·1, 67·5). One patient in group A (71 years old) and two patients in group B (87 and 73 years old) died from causes unrelated to heart disease (cancer n=2, septicemia n=1) during follow-up.

Follow-up durations in groups A and B patients were 40–7 months (17·7, 66·8) and 51–6 months (29·3, 73·1) (P=ns), respectively. Twelve patients (20·6%) in group A and 34 (28·8%) in group B had recurrences (P=ns). In group A, 10 patients had one syncopal recurrence, and two patients had two or more. In group B, 24 patients had one syncopal recurrence, and 10 had two or more. Compared to patients free of recurrences, those patients with recurrences suffered more syncopes before head-up tilt test (4·5 (3, 12) vs 3 (1, 5); P=0·002, respectively) but there were no differences in gender, age, asystolic pause occurrence or duration, timing to asystole during head-up tilt test or follow-up duration. Seven patients of group A and 15 of group B had only one syncope before undergoing head-up tilt test. During follow-up, no difference was noted compared with other patients of both groups.

The occurrence of new syncopal events during follow-up was not dependent on the presence of asystole, or the chosen therapy. In the first therapeutic approach, 2/8 patients (25%) treated with pacemakers, 18/62 patients (29%) treated with drug therapy and 26/106 patients (25%) who received only advice, suffered recurrences. The Kaplan–Meier analysis (Fig. 2) shows a
mean time free of recurrence of 92·6 ± 6·4 months vs 82·6 ± 4·7 months respectively, in groups A and B (P=ns), and a cumulative probability of no recurrence of 70·7% vs 66·7% (P=ns) during the follow-up.

**Discussion**

This study provides four main results. First, although asystole during head-up tilt test occasionally causes considerable concern, no cardiac deaths were observed, and consequently such finding does not imply a ‘malignant’ outcome. Second, the presence of asystole during head-up tilt test does not signify a tendency to syncope recurrence. In addition, most of the patients with recurrences had just one new syncopal episode. Third, pacemaker or drug therapy does not significantly influence outcome. Outcome seems to correlate to the previous number of syncopal episodes but not to gender, age, asystole occurrence, asystole duration, timing to asystole during head-up tilt test, or follow-up duration. Finally, tilting protocol (angle) may influence the time until and incidence of asystole during head-up tilt test.

**Prevalence and duration of asystole**

Previous reports have documented the occurrence of prolonged asystole during head-up tilt test. In 1989 Fitzpatrick and Sutton described a 10% incidence of asystole usually with hypotension. At a later date, the same authors published a study on 37 patients who underwent pacemaker implantation. This collective report included 11 patients with asystole lasting longer than 4000 ms. From those 11 patients, eight suffered recurrences. In accordance to our observations, these data do not suggest a beneficial outcome from pacing treatment. Later, Sra et al. reported six asystolic events (8·5%) in a group of 70 patients with an abnormal head-up tilt test. In addition, Dhala et al. found that from 209 consecutive patients with a history of syncope and abnormal head-up tilt test, 19 patients (9%) presented an asystole lasting ≥5000 ms. Furthermore, Grubb et al. described an asystolic response (>4000 ms) in 10 (20%) of 50 patients with recurrent syncope, whereas Brignole et al. reported on 28 patients (18%) with asystole (≥3000 ms) among 152 consecutive patients. Deal et al. described a lower (4·5%) incidence of asystole (≥5000 ms) among 398 consecutive paediatric patients. In Spain, Pérez-Paredes et al. published their experience with a cohort of 12 patients with asystole. However, they do not specify the prevalence of asystole in relation to the population studied.

Our study is the largest (n=58) cohort of patients with asystolic events out of a total of 1322 consecutive patients (4·3%) in whom head-up tilt test was performed. If we had defined asystole using a cut-off point of 4000 or 5000 ms, then this event would have been considered to occur in 48 and 43 patients, respectively. Interestingly, the main findings of the study in relation to follow-up did not change. The occurrence of prolonged pauses on head-up tilt test, do not correlate with the clinical presentation of initial symptoms, or with a worst prognosis during follow-up. From our data, the proportion of ventricular asystole is significantly greater during isoproterenol (tilting angle of 80°) than during the Westminster protocol (tilting angle of 60°): 6·5% vs...
isoproterenol). However, using isoproterenol (tilting non-asystolic group during a follow-up of 17 months) we did not confirm these expectations as our responses were similarly variable (mixed, cardioinhibitory and vasodepressor responses) comparing both protocols. Furthermore, our data suggest that the angle of tilting and the necessary time to change to the Trendelenburg position might be implicated in the incidence of the asystole.

Our findings and data of other authors indicate that the return to the supine position after syncope development is usually enough to allow recovery of spontaneous sinus rhythm, normalization of blood pressure and termination of the event. There is a lack of data on the relationship between changing the tilt-table to the supine or Trendelenburg position and duration of asystolic events. In our case, it takes 12 and 15 s to tilt the table from a 60°- and 80°-angle to Trendelenburg (−20°), respectively. If an asystole occurs, it usually does so at an early stage of the head-up tilt test and is almost always accompanied by syncope, which usually lasts until Trendelenburg conditions have been achieved or longer. Thus, lowering of the tilt-table should be done as fast as possible. In this context, the ACC Expert Committee recommend that lowering the tilt-table from an angle of 60° to the Trendelenburg position should not exceed 10–15 s. Although there are several reports on head-up tilt test, this aspect, which in our opinion is of paramount importance, is almost never reported.

In our series, the duration of asystole did not significantly differ between either protocol (Westminster and isoproterenol). However, using isoproterenol (tilting angle of 80°), asystole appeared at a significantly earlier stage.

**Follow-up and treatment of patients with asystole**

There is a broad range of reported syncope recurrences between patients with asystole during head-up tilt test, which obviously depends on patient selection and follow-up duration. For example, Dhala et al. found that two of 19 patients (11%) with asystole suffered recurrences during a follow-up of 2.1 ± 1.4 years, whereas Pérez-Paredes et al. reported that recurrences occurred in four of 12 (36%) patients with the same characteristics during a mean follow-up of 34 ± 20 months. In addition, Deal et al. described an incidence of 22-2% among 18 paediatric patients under different therapeutic regimens during 31 months of follow-up. Furthermore, Brignole et al. reported recurrences of syncope in five of 28 patients (18%) with asystolic responses and in 10 of 28 patients (36%) in the non-asystolic group during a follow-up of 17 ± 14 and 16 ± 12 months (P=ns). These findings are in accordance with ours, which show no better outcome in those patients without asystole. During 40.7 months (17-7, 66-8), only 12/58 of our patients (20.6%) with asystole suffered syncopal recurrences (one episode n=10; mean time free of recurrence of 92.6 ± 6.9 months; cumulative probability of no recurrence of 70.7%). When follow-up data were compared to those patients without asystole during head-up tilt test no differences could be observed. In our opinion, this recurrence rate, and especially the absence of any cardiac deaths, suggest that the appearance of asystole during the tilt-table test does not imply a malignant outcome. In our series only the number of previous syncopal events influenced the outcome.

When treating patients with several previous syncopal episodes the aim must be to avoid even one episode over many years of follow-up. Menozzi et al. implanted a specially designed pacemaker able to detect and store all asystolic episodes lasting 3 to 6 or >6 s in 23 patients. Only two of those patients had asystole during head-up tilt test. Interestingly, one of the two patients had several pauses (30 pauses of 3 to 6 s and three pauses >6 s) during follow-up, while the other had just one pause (3 to 6 s) and no syncopal recurrence.

Treatment of vasovagal syncope is a matter of controversy. Based on our findings since June 1995, we first recommend education in the form of advice, as described above, although patients and their physicians are informed in detail about the therapeutic options and our own experience about outcome. As recommended by Di Girolamo et al., education may include a tilting training programme, but we do not use it. We only recommend drug or pacing treatment in those patients with neurocardiogenic syncope who have suffered recurrences after an abnormal head-up tilt test despite the type of pathological response during the tilt-test. The pharmacological approach to vasovagal syncope has been recently questioned in two double blind, randomized, placebo-controlled trials that show a similar efficacy for etilefrine and placebo, and atenolol and placebo. Our own experience is in accordance with these data.

Initially, the Westminster Hospital group considered the appearance of bradycardia and asystole during the head-up tilt test sufficient for implanting a pacemaker. These patients were thought to have a worrisome outcome. At first we also used that approach. Now we have come to the conclusion that there is no definitive therapy since untreated patients in our study present a similar outcome to patients receiving pacemaker or drug therapy. In addition, two recent randomized trials of permanent cardiac pacing for the prevention of vasovagal syncope have been published. The first of these studies focused on the number of previous syncopes, but not on asystole duration. The authors conclude that ‘it would be reasonable to consider implanting a pacemaker in highly symptomatic patients with frequent vasovagal syncope who also have a relative bradycardia on tilt-table testing’. However, syncope recurrences occurred in 19 of 27 patients without and in 6 of 27...
patients treated with pacemakers\(^{[47]}\). Recently, Sutton et al.\(^{[48]}\) reported the results of a multicentre randomized trial. They conclude that in a limited selected group of patients with a cardioinhibitory response during tilt-test, DDI pacing with hysteresis reduced the likelihood of syncope with maintenance of benefit over time. Several differences exist between this and our study. The main one is that we present a consecutive and larger cohort of patients, whereas these authors report on a highly selected collective of 42 patients included over a period longer than 6 years from 18 participating centres. As the authors recognize, it is likely that only the ‘worst’ or ‘more severe’ cases were included. Interestingly, pacemaker therapy was not superior to ‘no therapy’ in preventing tilt-induced syncope during repeat tilt testing performed within 15 days of enrolment\(^{[48]}\), as also indicated by previous authors\(^{[18]}\).

This short-term outcome may not necessarily be identical to spontaneous long-term outcome. However, it makes it difficult to understand the mechanisms of syncope and the preventive mechanisms of pacemakers in this context. Studies that are not blinded (e.g. pacemaker implantation)\(^{[47,48]}\) cannot exclude a bias in assessment of outcome and a psychological benefit (‘placebo effect’) of pacemaker therapy. The reason for the decrease in syncope recurrence rate after diagnostic procedures, even in untreated patients, might indicate that syncopes occur in clusters or that patients learn to recognize prodromes and how to avoid the events, which is what our patients were systematically taught to do. Our data indicate a relationship between recurrences and the number of previous syncopes but not the chosen therapy. Thus, in agreement with other authors\(^{[5,8,9,11]}\) and considering our large cohort of patients (with a mean time free of recurrence of 92·6 months and without any cardiac death), we do not believe that pacemakers should be considered routinely as first choice therapy. This is substantiated by the fact that we and other authors (e.g.\(^{[48]}\)) document a benign outcome unrelated to therapy. However, the recurrence rate of syncope (with any strategy) indicates the need for better identification of those individuals who might benefit from specific therapeutical approaches. This aim will probably only be achieved after better understanding the pathophysiological mechanisms of syncope and identification of specific subgroups of patients.

**Limitations**

Treatment of patients was not randomized but chronologically (10 years) adapted based on experience. Thus, first the theoretically safest approach (pacemaker) was undertaken for ethical reasons. However, the experience suggests that the initial treatment is not necessarily the best. During follow-up, the occurrence of pre-syncpe is not evaluated because an accurate and objective evaluation would not be possible.

**Conclusions**

(1) Asystole during head-up tilt test does not imply a malignant outcome although recurrences occur; (2) pacemaker or drug therapy do not significantly influence outcome which correlates to the previous number of syncopal episodes but not to gender, age, asystole occurrence, asystole duration and timing to asystole during head-up tilt test; (3) tilting protocol (angle) might influence time to and incidence of asystole during head-up tilt test.

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