Epidemiology, Clinical Features, and Follow-Up of Patients With Syncope and a Positive Adenosine Triphosphate Test Result

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OBJECTIVES We sought to evaluate epidemiology, clinical features, and outcomes of patients with syncope and an abnormal response to adenosine triphosphate (ATP).

BACKGROUND Syncope remains of unknown origin in almost 30% of the patients. Injection of ATP induces in some of these patients, but not in control patients, a ventricular pause ≥ 6 s.

METHODS Patients with syncope of unknown origin had an intravenous injection of 20 mg of ATP. All patients had a tilt test.

RESULTS Among 214 patients, 19 (8.9%) had a positive ATP test result. The proportion of positive test results was higher (p < 0.002) in women (14.3%) than in men (2.2%). Ten patients (4.7%) had positive ATP and tilt test results. These patients (exclusively women) were older (p < 0.05) at the time of their first syncope than the 67 patients with a negative ATP test result but a positive tilt test result. There was a trend for these two test results to be correlated (p = 0.07). Side effects were of short duration and benign. The mean duration of pauses was longer in women (p = 0.009). During a mean period of 31 ± 14 months, recurrences of syncope were reported in 25% of patients.

CONCLUSIONS The ATP test is a safe test with an “abnormal” result in <10% of patients with syncope of unknown origin. The profile of these patients is characteristic.

Even after an extensive evaluation, the diagnosis of syncope remains undetermined in approximately 30% of cases (1–4). It has been suggested that induction of ventricular pause after intravenous injection of adenosine triphosphate (ATP) could unmask the cause of spontaneous syncope (5,6). However, these data are based on a limited number of surveys published by two groups (5–7). The main objectives of the present study were to evaluate epidemiology, clinical features, and outcomes of patients with long ventricular pauses during ATP injection. The secondary goals were to analyze the safety of the test and its relationship with head up tilt test (HUT).

METHODS

Patient selection. Patients admitted consecutively for investigation of syncope diagnosed according to the guidelines of the European Society of Cardiology (8) were candidates for inclusion in this prospective study. However, only those with syncope of unknown origin (SUO) after an extensive evaluation were definitely included.

Management of patients with syncope. Patients underwent a systematic clinical investigation including careful history taking (9), measurement of blood pressure in an upright position, and an electrocardiogram. When this workup remained inconclusive, carotid sinus massage and 24-h Holter monitoring were performed. When this second line of investigations remained negative, according to the presence or absence of overt heart disease and/or electrocardiographic abnormalities, electrophysiologic study (EPS) or HUT was performed. The alternative investigation (EPS or HUT) was performed during the following step. Only patients with negative baseline evaluation and negative subsequent test results, including EPS when necessary, were included.

Protocol of investigations. Investigations were performed and interpreted according to recommendations (8). Only the protocol of the ATP test will be described in detail. Patients were investigated in the morning. The ATP and tilt tests were successively performed, and the delay between the two procedures was long enough to allow complete recovery after the first test.

ATP test. Patients were advised of the likelihood of face flushing but not of other possible side effects to avoid excessive emotional stress. Patients with asthma were excluded. Except for drugs known to interact with ATP, the usual treatment was continued.

Twenty milligrams of the drug was dissolved in 10 mL saline solution and injected as a bolus. Electrocardiogram and blood pressure were monitored before and for 2 min after the injection. Patients were asked to report all of their feelings, and they were carefully reported by the physician.

The longest recorded RR interval was measured by the same investigator blinded to other results. The ATP test result was considered positive when the maximum RR interval was ≥ 6 s (6). In all of our cases, the ventricular pause resulted from atrioventricular (AV) block.
The protocol of HUT in our laboratory is conventional. Its duration was planned for 45 min or until the patient showed syncope. At the end of the 45 min, 400 μg of glyceryl nitrate was administered sublingually and the tilt period was prolonged for 20 min.

Follow-up. Every patient in whom the maximum RR interval measured during the ATP test exceeded four seconds was prospectively followed up. This follow-up was obtained by questionnaire or telephone interview of the patient, his family, or the general practitioner.

Statistical analysis. The chi-square test was used to compare nominal parameters between the groups. Mean ages were compared by the Student t test. The mean number of syncopal episodes was compared by the non-parametric test of Mann-Whitney. The relationship between the HUT and ATP test was explored by the chi-square test.

RESULTS

Study group. During the study period, 214 patients (119 women) with SUO before HUT were recruited. The mean age of the study group was 59 ± 18 years (range, 19 to 90 years). Men were slightly younger (57 ± 17 years) than women (61 ± 19 years). As a consequence of syncope, 26 patients (12.1%) had a fracture and 9 patients (4.2%) reported a traffic accident.

Results of the ATP test. A positive ATP test result was observed in 19 patients (8.9%), who reported a mean number of 4.9 ± 2.6 (range, 2 to 15) previous episodes (Table 1). The first syncope occurred at a mean age of 64.5 ± 19.7 years, and they were 72.1 ± 15.9 years old at the time of the ATP test. The mean duration of the ventricular pause during ATP was 10.7 ± 11.1 s. Women (89.5%) had this significantly (p < 0.0006) more frequently than men (10.5%), and the proportion of positive ATP test results was higher in the subgroup of women than in the subgroup of men (14.3% vs. 2.2%, p < 0.002).

Results of HUT. A positive HUT was observed in 77 patients (mean age at time of first syncope, 52.2 ± 22.1 years, and 63.0 ± 16.9 years at time of HUT). A positive response was observed during passive HUT in 29 patients, and after nitrate challenge in 48 patients. The proportion of positive HUT was higher (p < 0.03) in women (48 or 62.3%) than in men (29 or 37.7%). However, when reported as the number of patients from each gender, the proportion of positive HUT results was no longer significantly different between women (40.3%) and men (31.9%).

Results of the ATP test in patients with a negative tilt test result. Among the 214 patients included, 77 had a positive HUT result, suggesting that syncope was vasovagal. Therefore, the remaining 137 patients (64%) could be
considered as having SUO. The ATP test result was positive in 9 of these 137 patients (6.6%). The mean number of previous episodes was 5.3 ± 2.7 (range, 2 to 15). The mean age of the 9 patients at time of the first syncope was 63.6 ± 10.9 years, and was 74.8 ± 10.9 years at the time of ATP test. The mean duration of ventricular pause during ATP was 7.9 ± 8.1 s. The number of women (7, or 77.8%) was higher (p < 0.06) than the number of men (2, or 22.2%). When reported as the number of patients from each gender among the 137 patients, the proportion of positive ATP test results remained higher in women (9.7% vs. 3.1%).

### Comparison between patients with only one positive test result
Results of the comparison among the 9 patients with only a positive ATP test result and the 67 patients with only a positive HUT result are listed in Table 2.

#### Results in patients with both test results positive
Overlap between the two tests was studied in the 10 patients (4.7%, all women) with both test results positive. The mean age at the time of the first syncope was 65.4 ± 19.6 years and was 69.7 ± 19.6 years at the time of evaluation. These values were not statistically different from those observed in the nine patients with a positive ATP but a negative HUT test result (Table 1). These 10 patients were significantly older (p < 0.05) than the 67 patients with a negative ATP but positive HUT test result. It seems that patients with positive ATP test results had approximately the same profile irrespective of the result of the HUT. Finally, 128 patients (59.8%) had both test results negative.

The relationship between the two tests was not significant, but a clear trend toward a positive association (p = 0.07) was observed: when the HUT result was positive (77 cases), the ATP test result was positive in 10 cases (13%), and when the ATP test result was positive (19 cases), the HUT result was positive in 10 patients (52.6%).

### Long-term follow-up of patients with prolonged asystole during the ATP test
Patients with a ventricular asystole lasting four seconds or more were prospectively followed up. The value of four seconds was chosen because a slight increase in the number of patients after this cutoff point was observed (Fig. 1). Forty-three patients were included: 16 because a ventricular pause lasting between 4 and 5 s, 8 between 5 and 6 s, and 19 ≥ 6 s. Sixteen patients had to be excluded: 14 because of pacemaker implantation and two because they died (pulmonary embolism and cancer). Three additional patients were lost to follow-up. Finally, 24 patients were followed up for a mean period of 29 ± 13 months (range, 5 to 49 months). Recurrences of syncope were reported in 6 patients (23%): 4 had ventricular pauses between 4 and 5 s, and two of 7 s. Among the 8 patients with a pause ≥ 6 s and followed up for 31 ± 14 months without treatment, 2 (25%) had recurrence of syncope.

#### Side effects of the ATP test
Side effects are reported in Table 3.

### Discussion
The main result of this study is that 6.6% of patients with SUO after an extensive evaluation including HUT had a long ventricular pause after injection of ATP. The percentage of abnormal ATP tests in patients with SUO varies from 41% (5), 28% (6), 15% (7), and 6.6% (present series). This rate is decreasing regularly over time even in series reported by the same group (6,7). Several explanations could be found, but differences in the criteria used to define SUO and in the criteria used to analyze the results of the test are

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**Table 2. Clinical Characteristics of the Patients According to the Results of ATP and HUT**

<table>
<thead>
<tr>
<th></th>
<th>ATP+, HUT−</th>
<th>ATP−, HUT+</th>
<th>P</th>
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<tbody>
<tr>
<td>n</td>
<td>9</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>7 (77.8%)</td>
<td>38 (56.7%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean age (yrs)</td>
<td>74.8 ± 10.9</td>
<td>62.0 ± 16.4</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean number of syncope</td>
<td>5.33</td>
<td>4.13</td>
<td>NS</td>
</tr>
<tr>
<td>Mean age at first syncope</td>
<td>63.6 ± 20</td>
<td>50.1 ± 16.4</td>
<td>0.07</td>
</tr>
<tr>
<td>Warning symptoms</td>
<td>6 (66.7%)</td>
<td>42 (62.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Vagal circumstances</td>
<td>7 (77.8%)</td>
<td>36 (53.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Fractures</td>
<td>1 (1.1%)</td>
<td>10 (14.9%)</td>
<td>NS</td>
</tr>
</tbody>
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ATP = adenosine triphosphate; HUT = head up tilt test; NS = not significant.

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**Table 3. Side Effects**

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Ventricular pause &gt;30 s</td>
<td>2 (0.9%)</td>
<td></td>
</tr>
<tr>
<td>Ventricular pause &gt;20 s, &lt;30 s</td>
<td>3 (1.4%)</td>
<td></td>
</tr>
<tr>
<td>Chest constriction</td>
<td>21 (9.8%)</td>
<td></td>
</tr>
<tr>
<td>Intense flush</td>
<td>50 (23.4%)</td>
<td></td>
</tr>
<tr>
<td>Flash + chest constriction</td>
<td>49 (22.9%)</td>
<td></td>
</tr>
<tr>
<td>Chest pain</td>
<td>8 (3.7%)</td>
<td></td>
</tr>
<tr>
<td>Diffuse paresthesia</td>
<td>8 (3.7%)</td>
<td></td>
</tr>
<tr>
<td>Hypotension &lt;70 mm Hg</td>
<td>14 (6.5%)</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>8 (3.7%)</td>
<td></td>
</tr>
<tr>
<td>Intense malaise</td>
<td>15 (7.0%)</td>
<td></td>
</tr>
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</table>
probably the most relevant factors that explain the higher positive rate of ATP test reported in the first series (5,6). In our study, we followed recent guidelines (8) to diagnose SUO and included more than 200 patients. These arguments support the fact that our proportion of patients with a positive ATP test result is probably close to the current everyday practice. However, several questions remain unsolved and should be answered before ATP tests gain complete acceptance.

Is the ATP test really safe? The observed side-effects were expected in most instances, of short duration, completely reversible, and not life threatening. However, induction of long ventricular pauses requiring limited resuscitation maneuvers in <1% of cases leads us to recommend the attendance of a physician during the test.

Does the ATP test select a “new category” of patients with syncope? Patients with SUO and a positive ATP test result were older and more frequently women than were patients with SUO and a negative ATP test result (7,10). These findings were particularly evident in our study. Furthermore, we found that patients were also older at the time of their first syncope and that women were more sensitive to injection of ATP (longer pauses within the normal range are observed in women). These demographic findings are of value when considering that patients with a positive ATP test result represent a distinctive group among patients with syncope.

Does a positive ATP test result suggest that a spontaneous syncope is an “ATP-sensitive” syncope? Patients with a positive ATP test result have a special epidemiologic profile, but this is only a weak argument. The reproducibility of the test is another parameter that has been studied and should be answered before ATP tests gain complete acceptance.

What are the outcomes of patients with “long pauses” during the ATP test? This survey was not designed to answer this question, and the proportion of patients lost to follow-up is so great as to substantially bias the results. However, the recurrence rate of syncope seems to be relatively low.

Relationship between ATP and tilt tests. Although we failed to show a significant link between ATP and tilt tests, we observed as others (7,12) an important overlap between the tests. This does not imply that they explore the same phenomenon, but that there is probably a relationship between the possible common underlying phenomena.

CONCLUSIONS
Injection of ATP is a safe procedure that discloses an “abnormal” behavior in approximately 7% of patients with SUO. The profile of these patients is clearly unique in that it includes almost exclusively older women, an argument to consider that “ATP-sensitive” syncope could be a separate entity. These results are relevant to design trials to assess the effectiveness of therapeutic strategies.

REFERENCES