Predictive value of presyncope in patients monitored for assessment of syncope

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Background The purpose of this study was to assess the diagnostic value of recording the cardiac rhythm during presyncope in patients undergoing monitoring for undiagnosed syncope.

Methods and Results Eighty-five patients (age, 59 ± 18 years; 44 men, 41 women) with recurrent unexplained syncope underwent prolonged monitoring with an implantable loop recorder. Patients were examined for syncope, which was either recurrent or associated with at least 2 presyncopal episodes. Patients had a mean of 5.1 ± 5.5 syncopal episodes in the previous 12 months, and 70% of patients had symptoms for >2 years. Sixty-two (73%) patients had recurrent symptoms during a 12-month follow-up period. Of 150 recurrent events captured by the implantable loop recorder, there were 38 (25%) episodes of syncope and 112 (75%) episodes of presyncope. Syncope alone recurred in 12 patients, presyncope in 25, and both in 16. An arrhythmia was present in 64% of syncopal events (bradycardia in 16, tachycardia in 2) versus 25% for presyncopal events (bradycardia in 7, tachycardia in 3, P = .001). An arrhythmia was detected in 9 (56%) of the 16 patients with both syncope and presyncope, which was present in all recorded episodes of syncope compared with 6 of 9 presyncope episodes. Patient-related failure to freeze the device after symptoms occurred in 21 (36%) of 59 syncopal events compared with 15 (12%) of 127 presyncope events (P = .0001).

Conclusions Syncope is more likely to be associated with an arrhythmia than is presyncope in patients undergoing extended monitoring. Presyncope is a nonspecific end point that is frequently associated with sinus rhythm. Patients undergoing extended monitoring for syncope should continue to be monitored after an episode of presyncope unless an arrhythmia is detected. (Am Heart J 2001;141:817-21.)

Syncope is a common condition that can be readily defined as a transient loss of consciousness with spontaneous recovery.1,2 Presyncope is even more commonly reported but is difficult to define specifically. This is reflected in the wide array of symptoms that patients report that are collectively considered presyncope, including lightheadedness, dizziness, vertigo, unsteadiness, and “spells.” These symptoms are often self-limited or remain unexplained after investigation.

Many patients assessed for syncope also have a history of presyncope, but the relation of the two is often uncertain. Because the predominant cause of syncope is a transient fall in blood pressure leading to cerebral hypoperfusion, it stands to reason that less severe or shorter duration of hypotension arising from the same cause may result in presyncope rather than syncope. However, presyncope may be less specific and unrelated to the mechanism of syncope. We have previously reported an analysis of extended monitoring in 85 patients with unexplained syncope.3 On the basis of 50 initial events, syncope was more likely to be associated with an arrhythmia than presyncope. This report examines the symptom-rhythm correlation during 150 syncopal or presyncopal events during long-term follow-up in this group.

Methods
Patient population

Patients with unexplained syncope after a history, physical examination, electrocardiogram, and ≥24 hours of ambulatory or in-hospital monitoring were approached to participate in a multicenter study with prolonged monitoring with an implantable (insertable) loop recorder (ILR) to determine the cardiac rhythm during spontaneous syncope. Details of this trial have previously been reported.3 Patients were eligible for the study if they had ≥2 syncopal episodes within the previous 12 months or a single episode with a history of multiple presyncopal episodes. Further cardiovascular testing based on clinical suspicion was permitted before enrollment. This included echocardiography in 70%, head-up tilt-testing in 49%, electrophysiologic testing in 43%, and a trial of a wearable loop recorder in 24%.

Syncope was defined as a transient loss of consciousness with spontaneous recovery, not requiring cardioversion or...
Defibrillation. For the purpose of this study, presyncope was defined as a transient alteration in level of consciousness without loss of consciousness. This encompassed episodes described by the patient as near loss of consciousness, dizziness, lightheadedness, weak spells, and feeling faint. Patients were excluded if they were unlikely to survive 1 year, were unable to give informed consent, had a previous implanted programmable medical device, were pregnant, or were female of childbearing potential and not using a reliable form of contraception.

Eighty-five patients with unexplained syncope were enrolled in the study (Table I). The mean number of syncopal episodes in the previous 12 months was 5.1 ± 5.5 (median, 3). The majority of patients had recurrent syncope for >2 years. The institutional review board or medical ethics committee at each study center approved the study.

Details of the ILR (Medtronic USA, Minneapolis, Minn) have previously been reported.3-6 In summary, the ILR is a 61 × 19 × 8 mm recording device with 2 sensing bipoles 37 mm apart within its shell. It weighs 17 g and has a volume of 8 mL, slightly smaller than a standard VVI pacemaker. The device continuously records a single-lead electrocardiographic signal in a circular buffer capable of retaining up to 42 minutes of compressed signal. The memory buffer is “frozen” by means of a hand-held activator provided to the patient at the time of device implantation. The resultant programming divides the memory to capture up to 3 events. For example, the longest single event programming utilizes compressed memory to store 40 minutes before activation and 2 minutes after. The episodes are then downloaded after interrogation with a standard pacemaker programmer (Medtronic 9790C).

After the device was implanted and programmed, the patient, along with a spouse, family member, or friend, was instructed in the use of the activator. Patients were instructed to activate the device in the event of syncope or presyncope. Follow-up was performed every 2 months for 1 year and after each symptomatic event. The device remained implanted to complete 1 year of follow-up unless the patient or investigator chose to remove it sooner. If the resultant diagnosis required implantation of a pacemaker, the device was removed at the time of pacemaker implantation.

Analysis
Continuous variables were compared by means of the Student t test, and categoric variables were compared by means of the chi-square test. A value of P < .05 was considered significant.

Results
Syncope or presyncope recurred in 62 (73%) patients during the 1-year follow-up period (Figure 1). The mean time to recurrence was 2.9 ± 3.6 months. A total of 150 events were frozen by 53 patients during the course of follow-up, including 38 (25%) syncopal episodes and 112 (75%) presyncopal episodes. Nine patients failed to activate the device after symptoms and did not obtain a symptom-rhythm correlation. Three patients died of causes unrelated to syncope before recurrence, 2 patients were lost to follow-up, and 2 patients had early device removal before symptomatic recurrence (infection in 1, local pain in 1). The remaining 17 (20%) patients did not have a recurrence, completed 1 year of follow-up, and underwent device removal. In the 53 patients who froze the device for at least 1 event during follow-up, syncope was the only recurrent symptom in 12 patients, presyncope alone recurred in 25 patients, and both syncope and presyncope recurred in 16 patients (Figure 2).

An arrhythmia was detected in 21 (40%) of the 53 patients who recorded a rhythm during recurrent symptoms, with bradycardia being the most frequent. Of the 18 patients with bradycardia (heart rate <50 beats/min), 13 underwent device removal and pacemaker implantation. Six of the 18 patients with bradycardia had heart rate slowing that the investigator interpreted as in keeping with the cardioinhibitory component of neurally mediated syncope. Five of those 6 patients had syncope; only 1 had presyncope. Four additional patients had relative slowing with a heart rate >50 beats/min and were considered to have neurally mediated syncope. Three patients had supraventricular tachyarrhythmias associated with recurrent symptoms. The remaining 32...
patients had sinus rhythm during symptomatic recurrence and completed follow-up.

In the 41 patients with presyncope, an arrhythmia was present during symptoms in only 10 (24%) patients, with bradycardia in 7 patients and tachycardia in 3. In contrast, an arrhythmia was detected during symptoms in 18 (64%) of 28 patients who had syncope, with bradycardia in 16 and tachycardia in 2 ($\chi^2 P = .001$, Figure 3). Excluding those patients with a clinical diagnosis of neurally mediated presyncope (n = 4) or syncope (n = 6), the difference remained significant (25% vs 59%, $\chi^2 P = .009$).

Sixteen patients had recurrence of both syncope and presyncope. An arrhythmia was detected at some point in 9 (56%) patients, with bradycardia in 7. In those 9 patients, all captured syncopal events were associated with an arrhythmia. In 1 patient with presyncope associated with bradycardia, syncope was associated with failure to activate the device. In 6 of those 9 patients, the same arrhythmia resulted in presyncope (tachycardia in 2, bradycardia in 4). Three patients had sinus rhythm during presyncope, with significant bradycardia associated with syncope during follow-up. These patients all received a pacemaker.

When all 150 symptomatic events were considered in the entire study population, the proportion of syncopal events that was related to arrhythmia was even lower (12%) compared with 43% of syncopal events ($\chi^2 P < .001$, Figure 3). When patients with syncope were compared with those with presyncope or those with both syncope and presyncope, there was no difference in age, sex, prevalence of heart disease, or time to recurrent symptoms (all $P > .6$).

Failure to appropriately “freeze” the device after symptoms occurred 36 times in 18 patients. In all except 1 case, the patient did not utilize the device activator because they were not carrying it or were unable to locate it. No instance was subsequently attributed to device failure. Failed activation occurred in 21 (36%) of 59 syncopal events compared with 15 (12%) of 127 presyncopal events ($\chi^2 P = .0001$). Nine of these patients had an appropriate freezing of the device after spontaneous symptoms on a different occasion. On 3 occasions, patients failed to freeze the device after syncope but were successful after presyncope. In 2 cases, multiple syncopal events were not captured, and sinus rhythm was noted during presyncope. This was not believed to be relevant to the clinical cause for syncope. In the third patient, sinus bradycardia was noted with recurrent presyncope. One patient failed to freeze the device during both syncope and presyncope.
Discussion

In this study, we have shown that presyncope is much less likely to be associated with a significant arrhythmia than syncope. Presyncope occurred 3 times as frequently as did syncope but was only associated with an arrhythmia in 12% of episodes compared with 42% for syncope. This suggests that presyncope is a nonspecific symptom that is not generally associated with an ominous arrhythmia. This may be explained by the nonspecific nature of the complaints that are collectively considered presyncope, unlike frank loss of consciousness, which is less equivocal.

These data also suggest that in many cases, syncope and presyncope may not represent differing severity of the same underlying cause but that syncope and presyncope are often causally unrelated. Although some episodes of presyncope may reflect the same disease process that leads to syncope, many episodes may represent the endemic nature of presyncopal type symptoms in the general population, with enhanced awareness of symptoms in the patient preconditioned by previous syncope leading to increased reporting. It is likely that many recorded episodes of presyncope were unrelated to the index syncopal event that led to enrollment in the study. Thus presyncope should not be considered a valid end point unless an arrhythmia is recorded. This observation is similar to that reported in patients with syncope undergoing Holter monitoring, in which syncope was similarly more likely to be associated with an arrhythmia.7 Patients who had presyncope should continue to be monitored to “rule in or out” an arrhythmia. In other settings in which testing does not provide a symptom-rhythm correlation, considerable clinical judgment is required to interpret the significance of presyncope in a patient investigated for syncope. This is particularly relevant during provocative head-up tilt or electrophysiologic testing, in which presyncope may occur during induced abnormalities but may be unrelated to the indication for testing.

The uncertain clinical significance of presyncope is borne out by the findings in the 16 patients with both syncope and presyncope. In 3 of these patients, sinus rhythm with presyncope may have led the investigator to conclude that an arrhythmia had been excluded when further monitoring documented bradyarrhythmia during recurrent syncope. This may suggest neurally mediated syncope and presyncope with a more prominent cardioinhibitory component during syncope. The distinction between primary and neurally mediated bradyarrhythmia can be very difficult. A P wave cannot be identified in 63% of patients with an ILR, precluding clinical certainty regarding the underlying cause of bradyarrhythmia.8 Ongoing development of the device and preimplant mapping are likely to improve P-wave detection.

A symptom rhythm correlation was obtained in 62% of patients during follow-up. The overall diagnostic yield of the ILR was superior to previous reports with the wearable loop recorder.8,9 This is probably related to the longer duration of monitoring and reduced patient error with an internal sensing and recording device. In this study, the incidence of failed activation was lower than reported for the wearable loop recorder.8,9 Both technologies rely on activation by the patient or an observer to freeze episodes. This was much more likely to take place after an episode of syncope than presyncope in our study. This finding is not surprising, given the greater degree of incapacitation associated with syncope leading to inability to locate or activate the device. Further development of automatic triggers and longer memory capabilities for all forms of loop recorders are likely to reduce the lower likelihood of symptom-rhythm correlation associated with syncope. In addition, persistent monitoring is likely to capture a subsequent event if the monitoring period is extended.

Limitations

This patient population is not necessarily representative of patients with presyncope seen during initial examination. These patients were assessed because of the high likelihood of recurrent symptoms associated with the absence of a diagnosis after conventional testing. As such, they represented the opportunity to observe multiple events during prospective follow-up. The prevalence of arrhythmias in this population may not be generalized to all patients with syncope and presyncope, in which arrhythmias are found in a smaller proportion of patients.1,2,10,11 Data on the frequency of presyncope before enrollment was not obtained. Although this may have been of interest, the presence of syncope is what typically propels the clinician into pursuing a diagnosis. Finally, the number of patients with both syncope and presyncope is relatively small, precluding conclusive assessment of the significance of presyncope in these patients.

Conclusions

Presyncope is much more common than syncope during follow-up of patients investigated for syncope and much less likely to be associated with an arrhythmia. The nonspecific nature of presyncope suggests that it is of limited clinical utility as a surrogate for syncope in establishing a diagnosis. Patients undergoing prolonged monitoring for syncope should continue to be monitored after a presyncopal episode unless an arrhythmia is detected.

References


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Appendix

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Single-day loading dose of oral amiodarone for the prevention of new-onset atrial fibrillation after coronary artery bypass surgery

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**Background** Various regimens have been proposed for the prevention of postoperative atrial fibrillation, including the use of intravenous and oral amiodarone. The purpose of this study was to determine the effectiveness of a single-day loading dose of oral amiodarone in prophylaxis of atrial fibrillation during the 7 days after coronary artery bypass surgery.

**Methods** We conducted a double-blind, randomized, placebo-controlled study encompassing 315 consecutive patients who underwent coronary artery bypass surgery. They received either amiodarone (159 patients) or placebo (156 patients). Therapy consisted of a single oral loading dose of 1200 mg of amiodarone 1 day before surgery, followed by the maintenance dose of 200 mg daily during the next 7 days. Only episodes of atrial fibrillation lasting more than 1 hour or associated with hemodynamic compromise were taken into consideration.

**Results** Overall, the incidence of atrial fibrillation was similar in patients who received amiodarone (31/159, 19.5%) and placebo (33/156, 21.2%) \((P = .78)\). However, amiodarone reduced the incidence of atrial fibrillation in elderly patients (age ≥60 years): it occurred in 20 of 75 (26.7%) patients on amiodarone and in 28 of 65 (43.1%) patients in the placebo group \((P = .05)\). There were no differences between the study groups regarding the postoperative intrahospital morbidity and mortality and the duration of hospital stay.

**Conclusions** A single-day loading dose of oral amiodarone (1200 mg) does not prevent postoperative atrial fibrillation in a general population of patients undergoing coronary artery bypass surgery. However, it appears that this regimen reduces the occurrence of postoperative atrial fibrillation in elderly patients. [Am Heart J 2001;141:e8.]

Acute effects of melatonin administration on cardiovascular autonomic regulation in healthy men

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**Background** Previous studies have suggested that melatonin, a major pineal hormone, possibly modulates the autonomic nervous system in animals. The aim of this study was to examine the effects of melatonin administration on heart rate variability (HRV) in human beings.

**Methods** In 26 healthy men, melatonin (2 mg) or placebo was randomly administered. Power spectral analysis of HRV and blood pressure monitoring were performed in the supine position before and 60 minutes after administration and in the standing position 60 minutes after administration. Plasma catecholamine levels were also assessed.

**Results** No differences in any baseline parameters were found between the two groups. Compared with placebo, melatonin administration within 60 minutes increased R-R interval, the square root of the mean of the squared differences between adjacent normal R-R intervals, high-frequency power, and low-frequency power of HRV and decreased the low-frequency to high-frequency ratio and blood pressure in the supine position (all \(P < .01\)). Plasma norepinephrine and dopamine levels in the supine position 60 minutes after melatonin administration were lower compared with placebo \((P < .05\) and \(P < .01\), respectively). Standing up resulted in the decrease of HRV and the increase of blood pressure and plasma catecholamine levels in both administration groups, and the differences between the groups found in the supine position disappeared.

**Conclusions** These findings indicate that melatonin administration increased cardiac vagal tone in the supine position in awake men. Melatonin administration also may exert suppressive effects on sympathetic tone. [Am Heart J 2001;141:e9]

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