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Circulation 2002;105;2741-2745; originally published online May 13, 2002;
DOI: 10.1161/01.CIR.0000018125.31973.87
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

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Background—In patients with syncope and structural heart disease, syncope is suspected to be attributable to a primary cardiac arrhythmia, but little is known of its mechanism when electrophysiologic study is unremarkable.

Methods and Results—We applied an implantable loop recorder in 35 patients with overt heart disease at risk of ventricular arrhythmia, because these were patients with previous myocardial infarction or cardiomyopathy with depressed ejection fraction or nonsustained ventricular tachycardia in whom an electrophysiologic study was unremarkable. During a follow-up of 3 to 15 months, syncope recurred in 6 patients (17%) after a mean of 6±5 months; in 3 patients, the mechanism of syncope was bradycardia with long pauses (sudden-onset AV block in 2 cases and sinus arrest in 1 case); in 1 patient, there was stable sinus tachycardia; and in 2 patients, who had chronic atrial fibrillation, there was an increase in ventricular rate. A total of 23 episodes of presyncope were documented in 8 patients (23%): no rhythm variation or mild tachycardia in 12 cases, paroxysmal atrial fibrillation or atrial tachycardia in 10 cases, and sustained ventricular tachycardia in 1 case. No patient died during the study period nor suffered from injury attributable to syncopal relapse.

Conclusions—The patients with unexplained syncope, structural heart disease, and negative electrophysiologic study had a favorable medium-term outcome with no case of death and a low recurrence rate of syncope without related injury. The mechanism of syncope was heterogeneous, and ventricular tachyarrhythmia was unlikely. **(*Circulation*. 2002;105: 2741-2745.)**

Key Words: syncope ■ electrophysiology ■ arrhythmia ■ heart diseases ■ electrocardiography

In patients with syncope, structural heart disease, and a negative work-up including an electrophysiological study, the mechanism of syncope remains largely unknown during the follow-up even if the outcome is more favorable than the patients with a positive electrophysiological evaluation.[1–4] In general, a negative electrophysiological evaluation is regarded as useful in identifying a subgroup of patients at low risk of death and of recurrence of symptoms.[1–4] In these patients, no recommendation for therapy exists in the present guidelines because of the lack of prospective studies, and a strategy of waiting and watching is commonly regarded as reasonable.

An implantable event monitor has recently become available and has been validated in patients with unexplained syncope.[5] The implantable loop recorder (ILR) is placed subcutaneously under local anesthesia and has a battery life of 15 to 18 months. The device has a solid-state loop memory, and, in the present version, the ECG of up to 40 minutes before and 2 minutes after activation can be stored.

In the present study, we implanted an ILR in patients with structural heart disease and negative electrophysiologic study to evaluate the natural history of these patients and obtain additional information on the mechanism of syncope.

Methods

The International Study of Syncope of Uncertain Etiology (ISSUE) is a multicenter international prospective study aimed at analyzing the diagnostic contribution of ILR in the following 4 predefined groups of patients with syncope of uncertain origin: (1) isolated syncope group, consisting of patients without structural heart disease or with minor cardiac abnormalities that were considered to be without clinical relevance and not suggestive of a cardiac cause of syncope, absence of intraventricular conduction defects, and negative complete work-up including tilt testing; (2) tilt-positive group, consisting of patients as above but with positive response to tilt testing; (3) suspected bradycardia group, consisting of patients with bundle branch block and negative electrophysiologic test; and (4) suspected tachycardia group, consisting of patients with overt heart disease and negative electrophysiologic test. The patients in the present study belong to the subgroup of patients with suspected

Received January 31, 2002; revision received March 29, 2002; accepted March 29, 2002.

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*A complete list of investigators appears in the Appendix.

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Circulation **is available at http://www.circulationaha.org** **DOI: 10.1161/01.CIR.0000018125.31973.87**

tachycardia. The results of the other subgroups have already been published.[6,7]

Study Protocol

This group included all patients with overt heart disease at risk of ventricular arrhythmia, because these were patients with previous myocardial infarction or cardiomyopathy with depressed left ventricular ejection fraction or nonsustained ventricular tachycardia in whom an electrophysiologic study did not induce sustained monomorphic ventricular tachycardia, with the exception of the patients with bundle branch block, because these latter were evaluated separately.[7]

Patients were included in the study only if a careful history, physical examination, baseline ECG, carotid sinus massage, echocardiogram, 24-hour ambulatory monitoring, and complete electrophysiologic study were not diagnostic of the etiology of syncope. With the exception of the patients with bundle branch block, the study group can therefore be considered representative of the patient population affected by overt heart disease and unexplained syncope.

The electrophysiologic study included measurement of the sinus node recovery time; measurement of the HV interval at the baseline and under stress by incremental atrial pacing and, if the baseline study was inconclusive, pharmacological provocation with slow infusion of ajmaline (1 mg/kg IV); and assessment of the inducibility of supraventricular and ventricular arrhythmia. In accordance with present guidelines,[8] the electrophysiologic study was considered diagnostic, and, therefore, patients were excluded from the study in the following cases: (1) sinus bradycardia and abnormal sinus node recovery time; (2) baseline HV interval of ≥70 ms, 2nd or 3rd degree *His*-Purkinje block demonstrated during incremental atrial pacing, or high-degree *His*-Purkinje block elicited by intravenous administration of ajmaline; (3) induction of sustained monomorphic ventricular tachycardia; or (4) induction of rapid supraventricular arrhythmia that reproduced hypotensive or spontaneous symptoms.

When patients were deemed eligible, an ILR (Reveal, Medtronic) was implanted subcutaneously. The recommended programed mode was 1 event 21 minutes before activation and 1 minute after activation. Patients were instructed to activate the device after every episode of syncope or presyncope. The records of all episodes were retrieved, printed, and analyzed by investigators in each center and re-evaluated by the 3 members of the Event Committee.

End Points

The primary end point of this study was the analysis of the electrocardiographic tracing obtained during the first syncopal episode that was correctly recorded by the device. Secondary end points were the study of the natural history of the patients, which included major clinical events and total prevalence of syncopal and presyncopal recurrences.

Statistical Methods

Comparison between proportions was made by Fisher's exact test; the time to the onset of the events was analyzed by means of Kaplan-Meier survival curves.

Results

Clinical Characteristics of Patients

From March 1998 to November 2000, 35 patients were included. Patients were seen at the outpatient clinic every 3 months and were followed up until the primary end point was reached, the battery of the ILR ran down, or the patient died; no patient was lost to follow-up. The patients' characteristics are shown in Table 1. The mean follow-up was 16±11 months; follow-up was completed in October 2001.

TABLE 1. Patients' Characteristics

No. of patients	35
Mean age, years	66±13
Sex, male	31 (89%)
History of syncope	
Duration of syncope, y (median, interquartile range)	1 (1–3)
No. of syncopes during last 2 years (median, interquartile range)	2 (1–4)
Patients with presyncopal episodes during the last 2 years	18 (51%)
Trauma (total)	25 (71%)
Severe trauma (wounds, fractures)	2 (6%)
No warnings	23 (66%)
Vasoactive therapy at the time of the index syncope	26 (74%)
Antiarrhythmic therapy at the time of the index syncope	5 (14%)
Associated structural heart disease	35 (100%)
Ischemic, previous myocardial infarction	17
Ischemic, no myocardial infarction	3
Hypertrophic	9
Dilated	5
Valvular	1
Heart failure	3 (9%)
Mean ejection fraction	47±17
Ejection fraction <30% (echocardiogram)	2 (6%)
Nonsustained ventricular tachycardia on Holter recording	16 (46%)
Permanent atrial fibrillation	8 (23%)
Electrophysiologic study	
Baseline HV interval length, ms	49±8
Maximum HV interval after Ajmaline infusion (13 pts), ms	69±14
Induction of polymorphic ventricular tachycardia or fibrillation	8 (23%)
Sinus node recovery time >1500 ms	0 (0%)
Tilt testing, positive response	2/31 (6%)

Primary End Point

An ILR-documented syncopal event occurred in 6 patients (17%) after a mean of 6±5 months (Figure 1). The actuarial estimate of syncopal recurrence was 9%, 12%, and 19% at 3, 9, and 15 months, respectively (Figure 2). In 3 patients, the mechanism of syncope was bradycardia; in 2 cases, there was a sudden-onset AV block with a long ventricular pause of 6

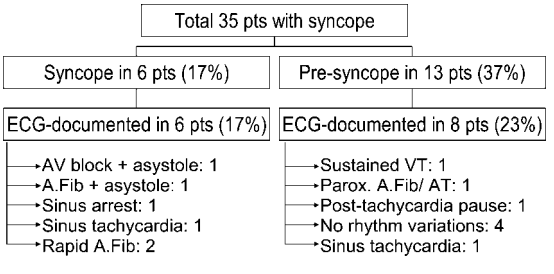

Figure 1. Events observed during the study period.

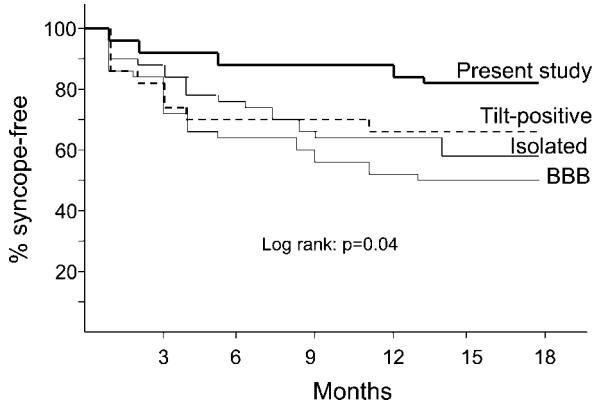

Figure 2. Kaplan-Meier estimates of the probability of remaining free of syncope. The estimates of the present study are compared with those calculated in the other previous groups of patients of the ISSUE study, namely those with isolated syncope,[6] positive tilt testing,[6] and bundle branch block.[7]

seconds and 13 seconds; in 1 case, there was an initial sinus tachycardia followed by progressive sinus bradycardia and finally a long sinus arrest of 27 seconds in duration. In 1 patient there was stable sinus tachycardia of 120 bpm. In 2 patients who had chronic atrial fibrillation, there was an increase in ventricular response at the time of loss of consciousness. Questioning of a witness to the recorded episode of one of these latter patients allowed diagnosis of an epileptic attack, thus clarifying the mechanism of the loss of consciousness.

Secondary End Points

Presyncope occurred in 13 patients (37%). A total of 23 episodes were documented in 8 patients (23%) (Figure 1). The most frequent finding, which was observed in 12 cases, was no rhythm variation or mild tachycardia. There were also 10 episodes of paroxysmal atrial fibrillation or atrial tachycardia; in 2 of these, the end of the arrhythmia was followed by a long pause of 6 seconds and 13 seconds in duration. Finally, 1 case was attributable to sustained ventricular tachycardia at a rate of 220 bpm.

A high reproducibility was observed in the 7 patients who had multiple events recorded. Multiple syncopal documented episodes occurred in 3 patients: 1 patient had 3 episodes of AV block with a long ventricular pause, 1 patient had 3 episodes of increased heart rate during chronic atrial fibrillation, and 1 patient had 2 episodes of stable sinus rhythm. Multiple presyncopal documented episodes occurred in 4 patients: 1 patient had 4 episodes of sinus tachycardia, 1 patient, affected by chronic atrial fibrillation, had 5 presyncopal episodes without rate variations, 1 patient had 1 episode of paroxysmal atrial fibrillation and another episode of paroxysmal atrial tachycardia, and finally 1 patient had 6 episodes of paroxysmal atrial fibrillation, 2 of which were followed by a long pause.

Overall, ECG-documented syncope or presyncope occurred in 14 patients (40%). The recurrence was not predicted by type of heart disease, presence of nonsustained ventricular tachycardia on Holter monitoring and induction of polymorphic ventricular tachycardia, or fibrillation during electrophysiologic study (Table 2). The patient with ECG-documented sustained ventricular tachycardia had a dilated cardiomyopathy with an ejection fraction of 35%, nonsustained ventricular tachycardia on Holter monitoring, and negative electrophysiologic study. None of the 2 patients with ejection fraction ≤30% had events during the follow-up.

TABLE 2. Distribution of the 14 Patients With ECG-Documented Events According to Baseline Variables

	ECG-Documented Events, No. of Patients (%)	
Coronary artery disease	6/20 (30)	NS
No coronary artery disease	8/15 (53)	
NSVT on Holter	6/16 (37)	NS
No NSVT on Holter	8/19 (42)	
Polimorphic VT/VF induction	1/8 (12)	NS (0.07)
No induction	13/27 (48)	

NSVT indicates nonsustained ventricular tachycardia; VT, ventricular tachycardia, and VF, ventricular fibrillation.

Clinical Events

No patient died during the study period nor suffered from injury attributable to syncopal relapse. At the end of the study, a permanent pacemaker was implanted in 3 patients and an implantable defibrillator was inserted in 1 patient. Antiarrhythmic drugs were given to 4 patients, and an antiepileptic drug was given to 1 patient.

Discussion

The main result of this study is that the patients with unexplained syncope, overt heart disease, and negative electrophysiologic study had a favorable medium-term outcome with no case of death and a low recurrence rate of syncope without related injury. The mechanism of syncope was heterogeneous; it was never attributable to a ventricular tachyarrhythmia that was documented only once in a patient with presyncope. Moreover, apart from the 2 cases of sudden-onset AV block that suggest a cardiogenic mechanism, the findings were very similar to those observed in the patients with isolated syncope and in patients with positive tilt test[6] in whom the likely etiology was neurally mediated or dysautonomic. This was even more true for the episodes of presyncope, with no or mild variations of the patient's heart rhythm and paroxysmal atrial tachyarrhythmias being the most frequent findings. The incidence of syncopal recurrence was lower than that observed in the other groups of the ISSUE study, namely those with isolated syncope with a positive tilt testing and those with bundle branch block[6,7](Figure 1). The patients of these latter groups had a higher number and a longer duration of syncopes in their history that can explain the different recurrence rate[9]; however, the recurrence rate we observed is similar to that reported in the literature for patients with nondiagnostic electrophysiologic evaluation.[1–4]

These results are partly unexpected, because the population of this study belongs to a group of patients affected by previous myocardial infarction or cardiomyopathy with depressed ejection fraction or nonsustained ventricular

tachycardia in whom syncope is generally regarded as a potential factor predictive of high risk of adverse events and, in particular, of ventricular arrhythmia and sudden death. For example, in one study,[10] age ≥45 years, history of congestive heart failure, history of ventricular arrhythmias, and abnormal ECG (other than nonspecific ST changes) were identified to be predictive of adverse outcome. Ventricular arrhythmias or death within 1 year occurred in 4% to 7% of patients without any of the risk factors and progressively increased to 58% to 80% in patients with 3 or more factors. In a recent study,[11] heart disease was an independent predictor of cardiac cause of syncope, with a sensitivity of 95% and a specificity of 45%; by contrast, the absence of heart disease allowed exclusion of a cardiac cause of syncope in 97% of the patients. In a selected population of patients with advanced heart failure and a mean ejection fraction of 20%, the patients with syncope had a higher risk of sudden death (45% at 1 year) than those without (12% at 1 year); admittedly, the risk of sudden death was similarly high in patients with either supposed cardiac syncope or syncope from other causes.[12] Finally, in 8 studies[13–20] performed in highly selected high-risk patients with syncope treated with an implantable cardioverter defibrillator, spontaneous ventricular arrhythmias requiring device therapy were frequently recorded, thus indirectly suggesting the mechanism of syncope. Admittedly, these patients had very different characteristics from those in the present study. Indeed, almost all had severe systolic dysfunction with very depressed ejection fraction, and many had a ventricular tachycardia inducible during electrophysiologic study.

How to explain the differences with the present study? First, although affected by a definite heart disease, only a few patients had heart failure or low ejection fraction. It is well-known that patients with ventricular tachyarrhythmias have higher rates of mortality and sudden death, but the excess mortality rates depend on underlying heart disease; patients with severe ventricular dysfunction have the worst prognosis.[21] In patients with unexplained syncope, nonischemic dilated cardiopathy with severe systolic dysfunction (mean ejection fraction of 26%) treated with an implantable cardioverter defibrillator, the incidence of discharge of the device was 50% after 2 years and the relapses of syncope or presyncope were primarily attributable ventricular fibrillation; the patients with more severe cardiomyopathy (ejection fraction of 20%) were more likely to receive an appropriate shock.[13] Conversely, in 68 patients with less severe coronary artery disease with a mean ejection fraction of 42±16, Link et al[4] observed a low recurrence rate of syncope similar to that of the present study, and all 4 episodes of arrhythmias or death occurred in patients with ejection fraction <25%. Another study using ILR[22] included patients with structural heart disease as long as ejection fraction >35%, and its results are not dissimilar from those of this study. Second, our patients had performed a complete work-up, including a negative electrophysiologic study. In patients with coronary artery disease, the induction of sustained monomorphic ventricular tachycardia is well proven to be predictive of the same cause of the syncope.[16–18] Conversely, when cardiac investigations are unable to support the initial suspect of cardiac syncope, the outcome seems to be favorable even if the diagnosis of the cause of syncope remains unexplained.[1–4] Third, patients with bundle branch block were excluded. It has been shown that these patients have the highest rate of cardiogenic syncope, in particular AV block.[7] Fourth, in a multicenter trial, detailed history taking is problematic, and it is possible that a more detailed history taking could be helpful to suggest an etiology different from cardiac. Actually, questioning a witness to the recorded syncope of 1 of the patients with stable rhythm allowed diagnosis of an epileptic attack (partial temporal epilepsy), thus clarifying the mechanism of the loss of consciousness.

To summarize, even in patients with overt heart disease, syncope is not necessarily an ominous finding, and the outcome largely depends on the clinical features of the patients. It seems that only the inducibility of sustained ventricular tachycardia or a very depressed systolic function can predict a syncope attributable to ventricular arrhythmia, and, conversely, their absence may predict a more favorable outcome. The results of this study are consistent with those of Kapoor et al,[23] who showed that the presence of structural heart disease was the most important predictor of outcome independently of the cause of the syncope.

Several other important results arose from this study, including the following findings. First, half of syncopal recurrences were attributable to a long ventricular asystole. This figure is similar to the rate of 46% observed in the patients with isolated syncope and to the rate of 62% observed in the patients with positive tilt test[6] but was lower than that observed in patients with bundle branch block that was 89%.[7] Thus, this study also confirms that a severe bradycardia is the underlying common cause of syncope in all subsets of patients with unexplained syncope.

Second, in the absence of severe pump dysfunction, the presence of nonsustained ventricular tachycardia on Holter monitoring and the induction of polymorphic ventricular tachycardia or fibrillation during electrophysiologic study seem to be of little value for predicting syncopal events and, in particular, ventricular tachyarrhythmias (Table 2).

Third, an excellent reproducibility of responses was observed when multiple syncopal or presyncopal episodes were documented in the same patient. This finding has a potential impact on therapy.

Limitations

The study is quite small, and subgroups of patients with specific types of structural heart disease or specific features (Table 1) are even smaller. Thus, the failure to detect a significant difference in the subgroups may well be type II error.

Screening logs were not maintained throughout the trial, and an entrance bias cannot be excluded. Investigators might have selected the healthier patients and excluded those who were possibly sicker. This is suggested by the low number of patients with poor left ventricular function, even if the risk stratification based on the results of the electrophysiological study might have had an important role in the selection of healthier patients.

Practical Implications

An important point that is worth highlighting is that structural heart disease and syncope do not automatically equate to ventricular arrhythmias and high mortality. Patients with structural heart disease, well-preserved left ventricular function, and negative electrophysiological study seem to behave more like patients without structural heart disease in the etiology of syncope and prognosis. An ILR-guided strategy seems reasonable, with specific therapy safely delayed until a definite diagnosis is made. In accordance with this approach, 11% of our patients finally received a pacemaker or a defibrillator and another 14% received pharmacological therapy after their first documented syncope. In the other patients, any therapy seemed unnecessary for the period of the study. Some of these patients would probably have had a documented syncopal recurrence if the monitoring phase had been prolonged additionally. The usefulness of a very prolonged monitoring phase and the efficacy of therapy in suppressing additional syncopal recurrences remain to be proved. The practice of more aggressive therapy, such as the use of implantable defibrillator, should be limited to very selected high-risk patients with severe heart failure, low ejection fraction, and high pretest probability of tachyarrhythmic syncope.

Appendix

Participating Centers and Investigators (number of patients in brackets):

Ospedale S. Anna, Como: G.L. Botto, A. Sagone, M. Luzi (8); Hospital Virgen de las Nieves, Granada: L. Tercedor, M. Alvarez (5); Ospedale S. Maria Nuova, Reggio Emilia: C. Menozzi, N. Bottoni (3); Hospital Clinico Universitario, Valencia: R. Garcia-Civera, R. Ruiz, S. Morell (2); Hospital Clinico i Provincial, Barcelona: L. Mont, J. Brugada (1); Ospedali Riuniti, Lavagna: M. Brignole, P. Donateo, G. Gaggioli (1); Hospital Virgen del Rocio, Sevilla: F. Errazquin (1); Hospital Xeral de Vigo, Vigo: X. Beiras (1); Ospedale Civile, Bentivoglio: B. Sassone (1); Hospital de Basurto, Bilbao: J.M. Ormaetxe (1); Ospedale Civile, Piacenza: A. Capucci, G. Villani, F. Groppi (1); Ospedale Civile di Oglio Po, Casalmaggiore: A. Perrini, G. Pellinghelli (1); Ospedale Civile, Lugo di Ravenna: E. Tampieri (1); Ospedale Fatebenefratelli, Roma: A. Puglisi, P. Azzolini (1); Hospital 12 de Octubre, Madrid: F. Arrivas, M. Lopez-Gil (1); Ospedale Valduce, Como: G. Foglia Manzillo (1); Hospital Universitario La Paz, Madrid: J.L. Merino, R. Peinado (1); Ospedale S. Pietro Igneo, Fucecchio: A. Del Rosso (1); Hospital General Universitario, Murcia: A. Garcia-Alberola (1); Hospital Virgen de la Victoria, Malaga: J. Alzueta (1); and Hospital Del Mar: J. Delclós (1).

Steering Committee

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Event Committee

M. Brignole, C. Menozzi, and A. Moya.

Study Managers

S. Cavaglià, R. Migliorini, X. Navarro, and L. Rapallini.

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