Holter monitoring for syncope: diagnostic yield in different patient groups and impact on device implantation

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Summary

Background: Holter monitoring is routinely used in patients referred for the evaluation of syncope, but its diagnostic value in different patient groups is unclear, as is its impact on device implantation (pacemaker or cardioverter-defibrillator).

Aim: To determine the diagnostic yield of Holter monitoring in the routine evaluation of syncope, and its impact on subsequent device implantation.

Design: Retrospective record review.

Methods: We reviewed all Holter studies in patients referred with syncope between 2000 and 2005. Strict criteria were applied to determine whether a study was diagnostic. The diagnostic value of Holter monitoring (overall and in five subgroups: age, gender, structural heart disease, ejection fraction, medication) and its impact on the implantation of devices, were determined.

Results: Of 4877 Holter studies, 826 were performed in patients with syncope (age 72 ± 15 years): 71 (8.6%) were considered to explain the syncope. Structural heart disease, ejection fraction and age were significant predictors of a diagnostic study (all \( p < 0.01 \)), whereas gender and cardiac medication were not. A device was implanted in 33 patients (4.4%) whose initial Holter did not explain their syncope, after mean 7 months, whereas 45 patients (5.4%) received a pacemaker based on the Holter results (\( p = 0.32 \)).

Discussion: The overall diagnostic yield of Holter monitoring in the evaluation of syncope was 8.6%, with dramatic differences between subgroups. Our data suggest that the impact of Holter monitoring on device implantation is generally overestimated.

Introduction

Syncope, defined as a sudden temporary loss of consciousness accompanied by a loss of postural tone, is a problem often seen by physicians in clinical practice.\textsuperscript{1} In the Framingham Heart Study, 11% of the subjects had at least one syncopal episode during an observation period of 18 years.\textsuperscript{2} Syncope accounts for 1–3% of visits to emergency departments and as much as 6% of hospital admissions. The prevalence of syncope varies significantly between different patient groups, and may be as high as 25% in a nursing home population aged >70 years.\textsuperscript{3–6} Vasovagal syncope has a benign prognosis, whereas cardiac syncope can be a predictor of serious disease, with a five-year mortality approaching 50%.\textsuperscript{2} Arrhythmias are the most common cardiac cause of syncope, and include bradyarrhythmias (such as sinus node dysfunction), atrioventricular conduction disorders, atrial fibrillation with slow or rapid ventricular response, and ventricular tachyarrhythmias.

The important issue when evaluating patients with presumed syncope is to determine whether they have in fact experienced syncope.\textsuperscript{7} As the majority of syncopes occur unwitnessed, diagnostic evaluation is often carried out because of presumed syncope, and frequently includes Holter monitoring,
among other tests. The overall diagnostic yield of Holter monitoring reported in the literature is 1–20%. However, it strongly depends on the population studied, a fact frequently not taken into consideration when referring patients for Holter monitoring. In addition, little is known about its impact regarding the subsequent implantation of pacemakers and implantable cardioverter-defibrillators (ICDs), and the effectiveness of this procedure.

We analysed an unselected group of patients with syncope referred for a single 24-h Holter monitoring session, and determined the diagnostic yield of Holter monitoring, with a focus on different patient groups and the impact on device implantation.

**Methods**

The data for this study were collected between January 2000 and December 2005, and stem from both out-patient and in-patient services. All Holter studies performed in patients due to syncope were reviewed for significant arrhythmias as the cause of syncope. Medical records of the patients were used to obtain demographic data and details on medical history, cardiac medication, echocardiography, and on actions taken based on the results of Holter monitoring. Holter studies were performed for 24 h with a two-channel device (Schiller AG). A patient was considered to have structural heart disease if he had evidence of cardiomyopathy on echocardiography or had documented coronary artery disease or myocardial infarction.

Findings on Holter studies were classified as follows.

(i) A normal Holter study. Completely normal studies or studies with arrhythmias of no clinical significance, e.g. patients with occasional premature atrial or ventricular contractions, patients with known atrial fibrillation and appropriate rate control.

(ii) An abnormal Holter study unlikely to explain syncope, e.g. bundle branch block, second-degree AV block Mobitz type I or non-sustained ventricular tachycardia (≥3 beats, <30 seconds), which, in the absence of depressed left ventricular ejection fraction (LVEF), is a condition considered to have an excellent prognosis.

(iii) A Holter study considered to be diagnostic, with one of the following arrhythmias during monitoring that could be correlated to syncope or presyncope: second-degree AV block Mobitz type II or third degree AV block; sinus pauses ≥3 s; atrial fibrillation with slow ventricular response (<40 bpm while awake);

sustained ventricular tachycardia (>30 s); supraventricular tachycardia or atrial fibrillation at a rate of >175 bpm for >30 s.

Based on this approach, the diagnostic value of Holter monitoring, both overall and in five pre-specified subgroups (age, gender, structural heart disease, LVEF, medication), and its impact on the implantation of permanent pacemakers and ICDs, was determined.

In December 2006, a qualified study nurse contacted all patients who had received a device and who were still alive, to determine whether further syncopal episodes had occurred during follow-up.

**Statistical analyses**

All continuous variables were summarised as means ± SD. Comparisons were made using the $\chi^2$ statistic for categorical variables and a student’s t-test for continuous variables. A $p$ value <0.05 was considered significant.

**Results**

**Baseline characteristics**

Of the 4877 Holter studies performed during the study period, 826 (17%) were ordered for the evaluation of patients with syncope. The mean ± SD age of the patients was 72 ± 15 years (range 19–96). Female patients ($n = 445$, 75 ± 15 years) were significantly older than male patients (69 ± 16 years, $p < 0.0001$). Data on demographic and clinical characteristics are summarised in Table 1.

LVEF was available in 626 patients (76%); mean value was 57±10%. Almost half of the patients ($n = 375$, 45%) had either evidence of structural heart disease on echocardiography, documented coronary artery disease or myocardial infarction. Ischaemic heart disease was the most common cause of structural heart disease (23%), followed by hypertensive (12%), and valvular heart disease (6%). Other structural heart diseases such as hypertrophic and dilated cardiomyopathy were infrequent as demonstrated in Figure 1. The high percentage of patients with structural heart disease is also reflected by the medication (Table 1). Only 69 patients (8%) were without cardiac medication. The patients with structural heart disease had a mean LVEF of 53±12% (LVEF known in 338/375 patients, 90%). This was significantly lower ($p < 0.0001$) than in patients with no structural heart disease, who had an LVEF of 61 ± 5% (LVEF known in 288/451 patients, 64%).
Results of Holter monitoring

Of the 826 Holter studies, 714 (86%) were classified as completely normal. Forty-one (5%) were classified as abnormal, but unlikely to explain syncope due to non-sustained ventricular tachycardia. In 40 of these 41, all available clinical information warranted no further action. In the only patient with non-sustained ventricular tachycardia and an ejection fraction of less than 40%, an electrophysiological study was performed. A sustained ventricular tachycardia was induced and an ICD implanted, based on the results of the MUSTT trial. However, the non-sustained ventricular tachycardia had been known before and thus the Holter study was non-contributory. There were 71 Holter studies (8.6%) considered to explain syncope. Table 2 summarises these findings. The most common arrhythmias thought to be consistent with syncope were high degree AV-block, sick sinus syndrome, and atrial fibrillation with slow ventricular response. Two patients had orthodromic reciprocating tachycardia with an accessory pathway, one had AV nodal re-entry tachycardia. One patient with a severely depressed LVEF had a pacemaker-mediated tachycardia, which led to a significant haemodynamic deterioration due to pronounced cardiac dyssynchrony.

Table 1  Baseline characteristics

|                          | Number | Percentage |
|--------------------------|--------|------------|
| Total number of patients | 826    |            |
| Age (years)              | 72 ± 15|            |
| Females                  | 445    | 54%        |
| Structural heart disease | 375    | 45%        |
| LVEF                     | 57 ± 10|            |

Cardiac medication

| Drug                        | Number | Percentage |
|-----------------------------|--------|------------|
| Aspirin                     | 322    | 39%        |
| Anticoagulation             | 124    | 15%        |
| ACE-inhibitor/Angiotensin   | 306    | 37%        |
| receptor blockers           |        |            |
| Betablockers                | 273    | 33%        |
| Verapamil/Diltiazem         | 33     | 4%         |
| Diuretics                   | 256    | 31%        |
| Amiodarone                  | 41     | 5%         |
| Sotalol                     | 8      | 1%         |
| Class I anti-arrhythmic drugs | 0   | 0%         |
| Digoxin                     | 25     | 3%         |

Data are means ± SD or numbers (%) as appropriate. LVEF, left ventricular ejection fraction, known in 626 patients.

Figure 1. Prevalence and types of structural heart disease (SHD) in the studied patient population. Of the patients with CAD, 56% (107/191) had documented myocardial infarction. Three patients with pulmonary heart disease (cor pulmonale), one with a status after myocarditis and 20 with unclassified cardiomyopathy were included in the category of ‘other’ structural heart disease. CAD, coronary artery disease; HHD, hypertensive heart disease; VHD, valvular heart disease; H(O)CM, hypertrophic (obstructive) cardiomyopathy; DCM, dilated cardiomyopathy.

Table 2  Results of Holter monitoring (n = 826)

| Classification                      | Number | Percentage |
|-------------------------------------|--------|------------|
| Normal                              | 714    | 86.4%      |
| Abnormal not explaining syncope     | 41     | 5.0%       |
| Abnormal explaining syncope         |        |            |
| Total                               | 71     | 8.6%       |
| AVB                                 | 19     | 2.3%       |
| SSS                                 | 16     | 1.9%       |
| AVB with SSS                         | 4      | 0.5%       |
| AF with SVR                          | 19     | 2.3%       |
| AF with RVR                          | 8      | 1.0%       |
| SVT                                 | 3      | 0.4%       |
| VT                                  | 1      | 0.1%       |
| PMT                                 | 1      | 0.1%       |

Data are numbers (%). AVB, atrioventricular block; SSS, sick sinus syndrome; AF, atrial fibrillation; SVR, slow ventricular response; RVR, rapid ventricular response; SVT/VT, supraventricular/ventricular tachycardia; PMT, pacemaker-mediated tachycardia.

Subgroups

Table 3 shows the diagnostic yield in the five pre-specified subgroups. Structural heart disease, LVEF and age were significant predictors of a diagnostic Holter study, whereas gender and cardiac medication were not.

Table 4 shows the increasing diagnostic yield of Holter monitoring with age (p < 0.005). The mean LVEF in all the age groups, including all subgroups of patients with and without structural heart disease, was 52% or higher.

In 107 patients (13%) with a prior myocardial infarction (LVEF 44% ± 12%), there were 15 diagnostic Holter studies (14%), in one case documenting ventricular tachycardia. Only 3% of all patients (n = 26) had an LVEF < 35%. Of these, six (21%) had a Holter study explaining syncope; none was due to ventricular arrhythmia.
In a comparison of the 345 patients aged >60 years with structural heart disease to the 119 aged <60 years without structural heart disease, we found a diagnostic Holter study in 41 (12%) vs. 2 (2%) of the patients (p<0.001). In a subgroup of 73 female patients aged <60 years, there were no diagnostic Holter studies, nor were there any in the 42 patients aged 40 years or younger. However, there were 8 (20%) Holter studies explaining syncope in the 41 patients aged >90 years (p<0.0001).

**Impact on therapy**

**Patients with a diagnostic Holter study**

In 58/71 (82%) patients with a Holter study explaining syncope, the symptoms were due to bradycardia. Of these, 45 (78%) received a pacemaker; three with sick sinus syndrome became asymptomatic when their negative chronotropic drug was discontinued. Ten patients who were supposed to receive a pacemaker did not receive it due to unknown reasons or denied implantation of a device. The three patients with a supraventricular tachycardia underwent successful radiofrequency catheter ablation. Atrial fibrillation with rapid ventricular response was treated with rate control in seven patients and rhythm control in one. The only patient with sustained ventricular tachycardia was empirically prescribed amiodarone, as he refused the implantation of an ICD. The pacemaker-mediated tachycardia was relieved by reprogramming the device.

**Patients with a non-diagnostic Holter study**

Out of the 755 patients with a Holter study considered unlikely to explain syncope or normal, 33 patients (4.4%) had recurrent syncope and subsequently received a device 7 months (median) after the index Holter study. This rate is not different to the 5.4% of patients receiving a pacemaker on the basis of a Holter study explaining syncope (p=0.32). Five patients received the pacemaker based on the result of an implantable or external loop recorder, 26 received a device (24 pacemakers, 2 ICDs) due to a documented arrhythmia on a resting 12-lead ECG, and two received a pacemaker because of further unexplained syncopes.

**Follow-up of patients who received a device**

Of the 78 patients who had either received a device due to the first diagnostic Holter study or during follow-up, 34 had died by December 2006 and two could not be contacted. None of the remaining 42 patients experienced further syncopes after device implantation.
Discussion

Main findings

In our population of 826 patients referred for the evaluation of syncope, the overall diagnostic yield of Holter monitoring was 8.6%. The diagnostic yield varied greatly among subgroups; the presence of structural heart disease, depressed LVEF and advanced age were predictors for a diagnostic Holter result. The frequency with which patients received either a pacemaker or an ICD based on Holter results was similar to that of the patients who underwent device implantation after further syncopes during follow-up. None of the patients with a device experienced further syncope during follow-up, suggesting that the events leading to implantation had truly been arrhythmogenic.

As 63% of patients with a Holter study considered to explain syncope received a pacemaker, it could be argued that the impact of Holter monitoring on device implantation is considerable if the Holter study is diagnostic. However, in the whole population, nearly 10% of the patients received a device, with similar percentages based on the index Holter study (5.4%) and after further syncopes during follow-up (4.4%). This demonstrates the low additional impact of Holter monitoring on device implantation, a finding that has not been shown in previous studies.

Previous studies

Finding the cause of syncope may often pose a challenge even for the experienced clinician. Although the evaluation of syncope frequently leads to excessive use of diagnostic tests, no diagnosis is made in 25 to 50% of patients.\(^7,11,13,14\)

Several guidelines for the diagnostic evaluation of syncope have been published. However, they frequently do not relate well to clinical practice.\(^15,16\)

An important problem of Holter monitoring is that the symptom (syncope) seldom occurs during monitoring, and hence the recording of an arrhythmia that could potentially explain syncope is frequently used as the diagnostic criterion. One study found that an arrhythmia-related symptom (syncope or presyncope) during Holter monitoring was present only in 2% of patients, and more subjects (15%) had syncope or presyncope without an associated arrhythmia, which in fact might be considered a negative diagnostic clue.\(^17\) In one recent study, the diagnostic yield of 24-h Holter monitoring (defined as the correlation of serious arrhythmias with syncope or near-syncope) was 6%, reaching 12% when restricted to high-risk patients with structural heart disease and/or an abnormal ECG.\(^18\)

The results of the latter study are reflected in our data, with a similar diagnostic yield overall as well as in patients with structural heart disease. However, we studied the diagnostic yield in various subgroups and had a much wider range of 0 to 20%. Previous studies on Holter monitoring focused on younger patients, and included subjects with presyncope and dizziness. Given the relatively old age of our patient population, our data might even overestimate the diagnostic yield of Holter monitoring when applied to a younger population.\(^17,19\)

The role of loop recorders

The optimal duration of Holter monitoring has also been questioned. There is evidence suggesting that monitoring for 24 h may not be enough to identify important arrhythmias in patients with syncope, especially in selected patient groups. Monitoring may need to be extended to 48 h if the first 24 h of monitoring is normal.\(^19\) It seems obvious that this strategy potentially identifies more, but certainly not all relevant arrhythmias. The longer, the better’ seems a logical approach, and it is not surprising that a prolonged monitoring strategy using an implantable loop recorder is even more likely to provide a diagnosis in patients with unexplained syncope than testing with an external loop recorder;\(^20\) however, the setting in which this approach would still be cost-effective remains to be determined. Recently, a cost-effectiveness analysis of a randomised trial comparing external loop recorders to Holter monitoring in the evaluation of ‘community-acquired’ syncope, showed that external loop recorders can be an economically attractive alternative because of their markedly increased diagnostic yield.\(^21\) In our population, a prolonged monitoring strategy (external or implanted loop recorder) provided a diagnosis of a significant arrhythmia in only 5 of the 33 patients (15%) who received a device despite a negative index Holter study. This demonstrates that such an approach results in an aetiological diagnosis in some, but far from all cases, and a device was implanted in a much higher percentage of cases due to an arrhythmia documented on a 12-lead ECG.

Subgroups

As cardiac arrhythmias are mostly intermittent and intervals vary greatly, a normal Holter study certainly does not rule out an arrhythmic cause of syncope. Holter monitoring should not be used as a screening tool in patients with possible syncope, since its diagnostic value is limited, especially without proper patient selection.\(^22\) This is emphasised by the results of our analysis, in which
we found dramatic differences in its diagnostic value between subgroups. The diagnostic yield was very low in patients aged <60 years without structural heart disease (1.7%) and absent in female patients aged <60 years, as well as in all patients aged <40 years.

For widely available testing modalities such as Holter monitoring, patient selection is crucial in order to reach an acceptable diagnostic yield. This could be achieved at least to some degree by screening for the presence of structural heart disease. In one study, an abnormal resting 12-lead ECG proved useful as a screening tool to select patients.23

In our study, LVEF was preserved in patients with structural heart disease but significantly lower (53%±12%) compared to patients without structural heart disease (LVEF 61%±5%; p<0.0001). Structural heart disease and depressed LVEF (<50%) were associated with relatively high diagnostic yields of nearly 12% and 14%, respectively. However, this information may not always be available. The diagnostic yield was similar when only focusing on patients with a previous myocardial infarction (14%) and higher (21%) in patients with an LVEF of <35%. The one case of syncope due to ventricular tachycardia occurred in the former group. Ventricular tachyarrhythmias are important causes of syncope, especially in patients with an ischaemic cardiomyopathy and patients with significantly decreased LVEF. A 24-h Holter monitor is probably less likely to record ventricular arrhythmias due to their often sporadic nature. Therefore ventricular tachyarrhythmias might be significantly underestimated when relying solely on Holter monitoring to evaluate patients with ischaemic cardiomyopathy or significantly depressed LVEF who present with syncope. The assessment of this patient group warrants a much more comprehensive evaluation.

Age was a significant predictor of a diagnostic Holter study, with the highest yield (almost 20%) in patients older than 90 years. This accords with the observation that the prevalence of disorders of the conduction system increases with age. The diagnostic yield in patients without structural heart disease only increased to an above average level in patients aged >90 years. It reached a diagnostic yield of 8%, the overall average in our patient population, only above the age of 70 years. Younger patients and patients without structural heart disease probably benefit more from a prolonged monitoring strategy, as discussed above. However, this depends on the clinical situation, including the interval between events and the exact history.

Limitations

Our study has several limitations. We report data from a single centre, and patient selection and thus diagnostic yield could be affected by referral bias. Due to the retrospective design, we had to rely upon referring physicians regarding patient selection. The question as to whether a given Holter study was done in a patient with true syncope, a patient with presumed syncope or even in order to rule out serious arrhythmia cannot be answered. Although relatively strict diagnostic criteria were applied, the absence of a gold standard to validate a diagnostic study leaves us with some degree of uncertainty to whether the syncope leading to the Holter study was in fact caused by the arrhythmia recorded during monitoring.

Conclusions

The diagnostic yield of Holter monitoring for the evaluation of syncope and the impact on device implantation is generally overestimated. In our population, the likelihood of a diagnostic Holter study varied greatly between different subgroups, and was especially low in patients aged <60 years and/or without structural heart disease. This suggests that these patients should not undergo Holter monitoring to evaluate syncope.

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