

The Diagnosis of Cardiac Arrhythmias: A Prospective Multi-Center Randomized Study Comparing Mobile Cardiac Outpatient Telemetry Versus Standard Loop Event Monitoring

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Utility of Mobile Outpatient Telemetry. *Introduction:* Ambulatory electrocardiographic monitoring systems are frequently used in the outpatient evaluation of symptoms suggestive of a cardiac arrhythmia; however, they have a low yield in the identification of clinically significant but infrequent, brief, and/or intermittently symptomatic arrhythmias. The purpose of this study was to compare the relative value of a mobile cardiac outpatient telemetry system (MCOT) with a patient-activated external looping event monitor (LOOP) for symptoms thought to be due to an arrhythmia.

Methods and Results: The study was a 17-center prospective clinical trial with patients randomized to either LOOP or MCOT for up to 30 days. Subjects with symptoms of syncope, presyncope, or severe palpitations who had a nondiagnostic 24-hour Holter monitor were randomized. The primary endpoint was the confirmation or exclusion of a probable arrhythmic cause of their symptoms. A total of 266 patients who completed the monitoring period were analyzed. A diagnosis was made in 88% of MCOT subjects compared with 75% of LOOP subjects ($P = 0.008$). In a subgroup of patients presenting with syncope or presyncope, a diagnosis was made in 89% of MCOT subjects versus 69% of LOOP subjects ($P = 0.008$). MCOT was superior in confirming the diagnosis of clinical significant arrhythmias, detecting such events in 55 of 134 patients (41%) compared with 19 of 132 patients (15%) in the LOOP group ($P < 0.001$).

Conclusions: MCOT provided a significantly higher yield than standard cardiac loop recorders in patients with symptoms suggestive of a significant cardiac arrhythmia. (*J Cardiovasc Electrophysiol*, Vol. 18, pp. 241-247, March 2007)

loop recorder, event monitor, syncope, palpitations, arrhythmia

Introduction

A variety of methods can be used in the outpatient evaluation of symptoms suggestive of a cardiac arrhythmia. The diagnostic yield of these technologies for identifying clinically significant but infrequent, brief, and/or intermittently symptomatic arrhythmias, however, is low. Holter monitoring for 24–48 hours is typically employed, but has a diagnostic yield of only 15–28%, depending on symptoms and frequency.^{1–3} External, patient-activated loop recorders can

improve the diagnostic yield to up to 63%,⁴ but require appropriate patient activation during the recurrence of symptoms, which can limit their usefulness.⁵ Mobile cardiac outpatient telemetry (MCOT) allows patients to be monitored continuously for an extended period and has been effective in the diagnosis of clinically significant, symptomatic, and asymptomatic cardiac arrhythmias.⁶ This technology has the potential to reduce patient error, enhance diagnostic accuracy, decrease time to diagnosis, and improve patient care. The purpose of this study was to compare the relative value of a MCOT system with a patient-activated external loop event monitor for symptoms thought to be due to an arrhythmia.

Methods

Study Design

The study was a regional, 17-center, 300-subject, prospective parallel clinical trial with patients randomized to either standard patient-activated external loop event monitoring (LOOP) or to mobile automated cardiac outpatient telemetry for up to 30 days.

Equipment

Both LOOP and MCOT utilized cutaneous ECG harnesses and sensors that the patients wore continuously. Two lead

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ECG strips were acquired by the MCOT system, while most LOOP systems acquired a single ECG lead. LOOP subjects received standard devices, which stored retrospective and prospective rhythm strips, to activate in the event of symptoms. ECG data were then transmitted telephonically by the patient. Each center utilized the company or system that it typically employs for evaluating similar symptoms. Although an autotrigger algorithm is commercially available in many loop recorders, these recorders were not uniformly available at all centers. Only two sites utilized looping event recorders with an autotrigger algorithm in all of their randomized patients. Forty-nine subjects, or 16% of the randomized population, were from these two sites.

MCOT patients received a pocket-sized, wireless recorder/transmitter personal data assistant (PDA) and installation of a home internet base unit (CardioNet,[®] San Diego, CA, USA).⁶ Rhythm strips were recorded continuously and automatically transmitted wirelessly via an integrated cellular modem from the PDA per physician-predesignated thresholds, or when the patient activated the PDA screen to report symptoms. Electrograms were screened 24 hours a day by central station technicians, with immediate referral to the prescribing physician for evaluation of rate and rhythm changes and/or symptoms (daily reporting except in emergencies).

Patient Selection

This study was designed to evaluate patients in whom the investigator had a strong suspicion of an arrhythmic cause of their symptoms, but who were a diagnostic challenge. Inclusion criteria were: (a) a high clinical suspicion of a malignant arrhythmia, (b) symptoms of syncope, presyncope, or severe palpitations occurring less frequently than once per 24 hours (presyncope was defined as transient dizziness, lightheadedness, unsteadiness, or weak spells without loss of consciousness; severe palpitations were defined as palpitations that would warrant referral for cardiac monitoring), and (c) a nondiagnostic 24-hour Holter or telemetry monitor within 45 days prior to enrollment.

Exclusion criteria were NYHA Class IV heart failure, myocardial infarction within the prior three months, unstable angina, candidate for or recent valvular cardiac surgery, history of sustained ventricular tachycardia or ventricular fibrillation, complex ectopy defined as ventricular premature depolarizations (VPDs) ≥ 10 /hour with a documented ejection fraction $\leq 35\%$, subjects < 18 years of age, and a concomitant condition prohibiting completion of or compliance with the protocol.

All subjects provided informed consent and the protocol was approved by a local Institutional Review Board. A randomization sequence was generated by an independent source prior to the start of the study. The randomization was accomplished via a within-site randomization scheme. Sites were given randomization schedules. Investigators, other study personnel, and the subjects were not able to identify the treatment assignment prior to randomization to either CardioNet or standard loop event recorder.

Study Endpoint

The primary endpoint was the confirmation or exclusion of a probable arrhythmic cause of the patient's symptoms (syncope, presyncope, or palpitations). Investigators classified the

arrhythmias as either clinically significant or clinically insignificant and then evaluated the temporal relationship of any symptoms and the likelihood that a clinically significant arrhythmia caused the patient's presenting symptoms. Exclusion of an arrhythmic cause was determined if any reported symptoms were not associated with an arrhythmia, including a temporally related, clinically significant arrhythmia. Monitoring was considered nondiagnostic if patients remained asymptomatic with either no arrhythmia or only a clinically insignificant arrhythmia documented.

Secondary endpoints included time-to-diagnosis utilizing time-to-event methods, and proportion of subjects with clinically significant arrhythmias. Clinically significant arrhythmias were defined as pauses ≥ 3 seconds (excluding compensatory pauses following VPDs); complete atrioventricular (AV) block; Mobitz type-2 second-degree AV block; atrial fibrillation or flutter (AF/AFL) (symptomatic with ventricular response > 120 or < 35 beats per minute (BPM), asymptomatic > 150 or < 30 BPM); symptomatic bradycardia < 40 BPM in adults or age-appropriated lower normal limits; sustained (> 10 seconds) or symptomatic supraventricular tachycardia (SVT) > 120 BPM; ventricular tachycardia (VT) > 100 BPM and > 3 beats; and any arrhythmia requiring therapeutic intervention.

All tracings were reviewed by an independent academic electrophysiologist blinded to patient randomization and history. The diagnosis of the blinded independent electrophysiologist was used as the study endpoint for purposes of data analysis.

Statistics

The projected goal was enrollment of 300 patients to power the study to detect a 33% difference in the primary endpoint to evaluate MCOT versus LOOP in confirming or excluding the diagnosis of an arrhythmia as the cause of presenting symptoms. This provided a power of 80% for comparison, using a standard Chi-square test with alpha of 0.05 to assess statistical significance. All alpha values presented were prepared in this fashion. Kaplan–Meier analyses were performed to assess time to diagnosis and time to diagnosis of significant arrhythmia. Log rank tests were performed to evaluate differences between the cohorts. All study endpoints, including subgroup populations, were compared using Chi-square analysis. Patient demographics were analyzed by using ANOVA for age and Fisher's Exact test for categorical variables. Presenting symptoms were compared using Fisher's Exact test and the two-sample median test. Since this was a trial comparing diagnostic yields of two different technological approaches, the analysis was performed on those subjects with $> 80\%$ compliance, i.e., used the monitor for 25 days or more, unless a diagnosis was made.

The primary endpoint was counted once per patient, with subsequent primary endpoints during the monitoring period recorded as secondary endpoints. Subgroup analyses were performed for patients presenting with syncope/presyncope and for detection of clinically significant arrhythmias. Time to diagnosis was analyzed for all patients, those with clinically significant arrhythmias, and those presenting with syncope/presyncope. A subgroup analysis was performed of those sites that utilized looping event recorders with autotrigger algorithms.

TABLE 1
Patient Demographics

| Characteristic | Monitoring Method | | P Value |
|--------------------------------|-------------------|-------------------|---------|
| | MCOT (N = 134) | LOOP (N = 132) | |
| Gender, %male | 37.3 | 31.1 | NS |
| Age (SD), years | 57 (16) | 55 (16) | NS |
| Ethnicity or Race, n (%) | | | |
| Hispanic or Latino | 17 (12.7) | 25 (18.9) | NS |
| Black/African American | 15 (11.2) | 11 (8.3) | NS |
| White | 94 (70.1) | 93 (70.5) | NS |
| Other | 7 (5.2) | 3 (2.3) | NS |
| Missing | 1 (0.7) | 0 (0.0) | NS |
| Cardiac History, n (%) | | | |
| Hypertension | 70 (52.2) | 60 (45.5) | NS |
| Coronary Artery Disease | 22 (16.4) | 30 (22.7) | NS |
| Previous Myocardial Infarction | 6 (4.5) | 8 (6.1) | NS |
| Congestive Heart Failure | 8 (6.0) | 6 (4.5) | NS |
| Pacemaker | 7 (5.2) | 5 (3.8) | NS |

NS = nonsignificant.

Results

Patient Demographics

A total of 305 patients were randomized. We analyzed 266 patients who completed a minimum of 25 days of monitoring: 132 patients in the LOOP group and 134 patients in the MCOT group (the perprotocol population). Of the 39 nonperprotocol patients, 23 were in the MCOT group and 16 in the LOOP group. The most common reason for not completing the protocol was patient noncompliance (13 MCOT subjects and seven LOOP subjects), with seven patients finding the devices too difficult or cumbersome to use, seven patients describing an allergic reaction or skin irritation to the electrodes, and six patients stating that the monitors interfered with their work or travel. Other reasons for not completing the protocol included withdrawal of consent prior to receiving the device, inability to contact the patient for delivery of the device, and one patient who did not have adequate telephone service for using the MCOT device.

Demographics are shown in Table 1. There was no significant difference between groups in age, gender, or race. Patients were predominantly female with a mean age of 56 years, and of a diverse ethnic background. There was no significant difference between groups in patient history. Presenting symptoms are shown in Table 2, along with the mean number of episodes and their range prior to randomization. While the majority of patients had palpitations prior to randomization, 114 patients (43%) presented with either syncope or presyncope. Sixty-two of these patients used MCOT and 52 patients used LOOP. There was no significant difference in either demographics or cardiac history between patients presenting with syncope/presyncope or palpitations only.

Primary Endpoint

Classifications of the subjects by endpoint scenarios are shown in Table 3. A diagnostic endpoint was not determined for three subjects due to an independent cardiac outcome assessment not being performed. Scenarios 1 through 4 were considered as confirming an arrhythmic cause for the pa-

TABLE 2
Presenting Symptoms

| Subject Symptoms | Monitoring Method | | P Value |
|---------------------|-------------------|-------------------|---------|
| | MCOT (N = 134) | LOOP (N = 132) | |
| Presyncope, n (%) | 50 (37) | 41 (31) | NS |
| Median, (min, max) | 4.0 (1, >99) | 4.0 (1, >99) | NS |
| Syncope, n (%) | 23 (17) | 20 (15) | NS |
| Median, (min, max) | 1.0 (1, 10) | 2.0 (0, 5) | NS |
| Palpitations, n (%) | 105 (78) | 111 (84) | NS |
| Median, (min, max) | 10.0 (1, >99) | 10.0 (1, >99) | NS |

Median number of events per patient prior to enrollment; NS = nonsignificant.

tient's symptoms while scenarios 5 and 6 excluded an arrhythmogenic etiology. Scenarios 7 and 8 were considered a nondiagnostic result; these included subjects with no symptoms during the monitoring and no documented clinically significant arrhythmias. Mobile automated cardiac telemetry demonstrated a significant advantage over looping event monitors, with a diagnosis made in 88% of MCOT subjects, compared with 75% of LOOP subjects (Table 4, $P = 0.008$). There was a similar result in the subgroup of patients presenting with syncope or presyncope, with a higher diagnostic yield in the MCOT group (89% in MCOT subjects vs. 69% in LOOP subjects, $P = 0.008$).

The ability to detect or exclude a cardiac arrhythmia at the time of symptoms was similar in both groups. Simultaneous recording of an arrhythmia at the time of the patients symptoms (Table 3, scenarios 1 and 4) occurred in 40% of MCOT patients and 47% of LOOP patients (42% and 40%, respectively, in the syncope/presyncope subgroup). There was also a similarly large proportion of subjects who had symptoms, but without a temporally related arrhythmia (Table 3, scenarios 2, 5, and 6). In the MCOT group, there were 52 such subjects (39%), but 40 of the 52 subjects did have an arrhythmia documented at other times during their monitoring period. In 15 of these subjects, the arrhythmia was considered clinically significant. In the LOOP cohort, 36 subjects (27%) had symptoms without temporally related arrhythmias, but only nine subjects had an asymptomatic arrhythmia documented during the monitoring period, which could account for their symptoms. None of these arrhythmias were considered clinically significant. These results were similar in the syncope/presyncope subgroup, where 37% of the MCOT cohort and 27% of the LOOP cohort had no temporally related arrhythmias detected during symptoms. In the MCOT group, however, 20 of these 23 subjects had arrhythmias documented at other times, compared with only four of 14 LOOP subjects.

In the per-protocol population, there were 60 subjects (23%) who had no symptoms during monitoring, including 28 subjects (21%) in the MCOT group and 32 (24%) in the LOOP group. Twelve of the MCOT subjects were found to have an asymptomatic clinically significant arrhythmia that would account for their presenting symptoms, compared with no subjects in the LOOP group. For patients presenting with syncope/presyncope, a similar proportion of patients (25%) remained asymptomatic. In this subgroup, six of 13 asymptomatic subjects in the MCOT cohort had a clinically significant arrhythmia accounting for their presenting symptoms, compared with none of 16 LOOP subjects.

TABLE 3
Categorization of Subjects by Endpoint Scenarios

| All Subjects | | | | | | | |
|--|---------|-----------------------|---------|------------------------|------------|-----------------------|-----------------------|
| Scenario | Present | Symptoms Simultaneous | Present | Arrhythmia Significant | Diagnostic | Monitoring Method | |
| | | | | | | MCOT, n (%) (N = 133) | LOOP, n (%) (N = 130) |
| Confirmation/Exclusion | | | | | | | |
| 1 | Yes | Yes | Yes | Yes | Yes | 28 (20.9) | 19 (14.4) |
| 2 | Yes | No | Yes | Yes | Yes | 15 (11.2) | 0 (0.0) |
| 3 | No | — | Yes | Yes | Yes | 12 (9.0) | 0 (0.0) |
| 4 | Yes | Yes | Yes | No | Yes | 25 (18.7) | 43 (32.6) |
| 5 | Yes | No | Yes | No | No | 25 (18.7) | 9 (6.8) |
| 6 | Yes | — | No | — | — | 12 (9.0) | 27 (20.5) |
| Nondiagnosis | | | | | | | |
| 7 | No | — | Yes | No | No | 14 (10.4) | 6 (4.5) |
| 8 | No | — | No | — | — | 2 (1.5) | 26 (19.7) |
| Subjects Presenting with Syncope or Presyncope | | | | | | | |
| Scenario | Present | Symptoms Simultaneous | Present | Arrhythmia Significant | Diagnostic | Monitoring Method | |
| | | | | | | MCOT, n (%) (N = 62) | LOOP, n (%) (N = 51) |
| Confirmation/Exclusion | | | | | | | |
| 1 | Yes | Yes | Yes | Yes | Yes | 17 (27.4) | 8 (15.4) |
| 2 | Yes | No | Yes | Yes | Yes | 9 (14.5) | 0 (0.0) |
| 3 | No | — | Yes | Yes | Yes | 6 (9.7) | 0 (0.0) |
| 4 | Yes | Yes | Yes | No | Yes | 9 (14.5) | 13 (25.0) |
| 5 | Yes | No | Yes | No | No | 11 (17.7) | 4 (7.7) |
| 6 | Yes | — | No | — | — | 3 (4.8) | 10 (19.2) |
| Nondiagnosis | | | | | | | |
| 7 | No | — | Yes | No | No | 7 (11.3) | 5 (9.6) |
| 8 | No | — | No | — | — | 0 (0.0) | 11 (21.2) |

Present = presence or absence of symptoms/arrhythmia during the monitoring period; Simultaneous = symptoms that are temporally related to a recorded arrhythmia; Significant = an arrhythmia defined as Clinically Significant (see text); Diagnostic = recorded arrhythmia determined to be the most likely cause of the subject's presenting symptoms (palpitations, syncope or presyncope).

Although looping event recorders with an autotrigger algorithm were not required during this study, a post hoc analysis was performed of subjects who were enrolled at sites utilizing this type of monitor. These monitors were programmed to automatically record bradyarrhythmias, tachyarrhythmias, pauses, and irregular heart beats. Each monitoring company's standard parameters were used. Fifty of the 266 patients in the perprotocol population were evaluated: 24 subjects in the MCOT group and 26 subjects in the LOOP group. In this subgroup of patients, an arrhythmia was confirmed or excluded in 88% of MCOT subjects, compared with 46% in the LOOP cohort ($P = 0.002$). In subjects who remained asymptomatic throughout the monitoring period, a cardiac arrhythmia was

documented in nine of nine MCOT subjects and in five of 14 LOOP subjects. Despite the autotrigger algorithm, no patients in this LOOP subgroup were diagnosed with asymptomatic, clinically significant arrhythmias, whereas 50% of all MCOT patients in this subgroup were diagnosed as such.

Clinically Significant Arrhythmias

Table 5 shows the incidence of the previously defined clinically significant arrhythmias for the per-protocol population. MCOT was found to be superior to LOOP for confirming the diagnosis of these arrhythmias, detecting such events in 55 of 134 patients (41%), compared with 19 of 132 patients (15%) in the LOOP group ($P < 0.001$). There was a significant

TABLE 4
Primary Endpoint: Confirmation or Exclusion of an Arrhythmia

| Endpoint Outcome | Monitoring Method | | All Subjects | P Value |
|---|-------------------|-----------|--------------|---------|
| | MCOT | LOOP | | |
| All Patients Completing Protocol, n | 133 | 130 | 263 | |
| Confirmation or Exclusion, n (%) | 117 (88.0) | 98 (75.4) | 215 (81.7) | |
| Nondiagnostic, n (%) | 16 (12.0) | 32 (24.6) | 48 (18.3) | 0.008 |
| Patients with Syncope/Presyncope, n | 62 | 51 | 113 | |
| Confirmation or Exclusion, n (%) | 55 (88.7) | 35 (68.6) | 90 (79.6) | |
| Nondiagnostic, n (%) | 7 (11.3) | 16 (31.4) | 23 (20.4) | 0.008 |
| Patients at Sites with Autotrigger Loop Recorder, n | 24 | 26 | 50 | |
| Confirmation or Exclusion, n (%) | 21 (87.5) | 12 (46.2) | 33 (66.0) | |
| Nondiagnostic, n (%) | 3 (12.5) | 14 (53.8) | 17 (34.0) | 0.002 |

TABLE 5
Classification of Documented Arrhythmias in All Subjects

| Subjects with Arrhythmias | Monitoring Method | | All Subjects (N = 266) | P Value |
|---|-------------------|-------------------|---------------------------|---------|
| | MCOT (N = 134) | LOOP (N = 132) | | |
| Presence of a nonclinically significant arrhythmia, n (%) | 112 (84.2) | 67 (51.5) | 179 (68.1) | <0.001 |
| Presence of a clinically significant arrhythmia, n (%) | 55 (41.4) | 19 (14.6) | 74 (28.1) | <0.001 |
| Pauses, n (%) | 6 (4.5) | 0 (0.0) | 6 (2.3) | 0.014 |
| Complete atrioventricular (AV) block, n (%) | 0 (0.0) | 1 (0.8) | 1 (0.4) | NS |
| Mobitz type-2 second-degree AV block, n (%) | 1 (0.8) | 0 (0.0) | 1 (0.4) | NS |
| Atrial Fibrillation or Atrial Flutter, n (%) | 31 (23.3) | 10 (7.7) | 41 (15.6) | <0.001 |
| Symptomatic, ventricular rate > 120 BPM, n (%) | 10 (7.5) | 10 (7.7) | 20 (7.6) | NS |
| Asymptomatic, ventricular rate > 150 BPM, n (%) | 23 (17.3) | 0 (0.0) | 23 (8.7) | <0.001 |
| Symptomatic bradycardia < 40 BPM, n (%) | 0 (0.0) | 0 (0.0) | 0 (0.0) | NC |
| Sustained (> 10 seconds) or symptomatic supraventricular tachycardia (> 120 BPM), n (%) | 14 (10.5) | 5 (3.8) | 19 (7.2) | 0.036 |
| Ventricular tachycardia (> 100 BPM and > 3 beats), n (%) | 24 (18.0) | 4 (3.1) | 28 (10.6) | <0.001 |
| Any arrhythmia requiring therapeutic intervention, n (%) | 0 (0.0) | 0 (0.0) | 0 (0.0) | NC |
| Other, n (%) | 1 (0.8) | 0 (0.0) | 1 (0.4) | NS |

NC = not calculated; NS = nonsignificant.

advantage using MCOT in the detection of atrial fibrillation or flutter; both monitoring arms documented a similar percentage of patients with symptomatic atrial fibrillation or flutter (8% in both cohorts), but 17% of the MCOT group also had asymptomatic atrial fibrillation/flutter with rapid ventricular rates of > 150 bpm. Clinically significant arrhythmias were even more prevalent in patients with syncope or presyncope. In this cohort, a clinically significant arrhythmia was detected in 52% of the MCOT subjects, compared with 16% of the LOOP subjects ($P < 0.001$) (Table 6). Figure 1 shows a Kaplan–Meier event curve for the cumulative proportion of patients diagnosed with a clinically significant arrhythmia for the total study group (Fig. 1A) and the syncope/presyncope subgroup (Fig. 1B). The median time to diagnosis in the total study population was seven days (95% CI 4–11 days) in the MCOT group and nine days (95% CI 7–15 days) in the LOOP group. In the syncope/presyncope subgroup, the median time to diagnosis was six days (95% CI 3–16 days) and 10 days (95% CI 7–21 days), respectively. In the total population, 70% of the patients who had a clinically significant arrhythmia were diagnosed by the 15th day, regardless of monitoring method, but there was a much higher yield (29% vs 11% of

the total population on Day 15) in the MCOT group. Similar results were observed in the syncope/presyncope subgroup.

Discussion

Patients with symptoms of palpitations, presyncope, or syncope, and who are suspected of having a cardiac arrhythmia, can be difficult to diagnose. Ambulatory Holter monitoring is frequently employed as a diagnostic tool, but for infrequent symptoms, it has a historically low yield. Several studies have demonstrated the superiority of extended monitoring with looping event recorders.^{3,4} In a study by Kinlay et al.,⁷ 45 patients with intermittent palpitations were randomized for up to three months of cardiac event monitoring with a loop recorder, or 48 hours of Holter monitoring, and then crossed over to the other device. Loop recorders were more likely to provide a diagnosis than Holter monitoring, with a yield of 67% vs 35%. In a study of 100 patients with syncope or presyncope, Sivakumaran et al.,⁸ also demonstrated a higher yield with loop recorders. In this study, an arrhythmia was identified or excluded in 63% of the loop

TABLE 6
Classification of Documented Arrhythmias in Subjects with Syncope/Presyncope

| Subjects with Arrhythmias | Monitoring Method | | All Subjects (N = 114) | P Value |
|---|-------------------|------------------|---------------------------|---------|
| | MCOT (N = 62) | LOOP (N = 52) | | |
| Presence of nonclinically significant arrhythmia, n (%) | 55 (88.7) | 25 (49.0) | 80 (70.8) | <0.001 |
| Has clinically significant arrhythmia, n (%) | 32 (51.6) | 8 (15.7) | 40 (35.4) | <0.001 |
| Pauses, n (%) | 3 (4.8) | 0 (0.0) | 3 (2.7) | NS |
| Complete atrioventricular (AV) block, n (%) | 0 (0.0) | 1 (2.0) | 1 (0.9) | NS |
| Mobitz type-2 second-degree AV block, n (%) | 1 (1.6) | 0 (0.0) | 1 (0.9) | NS |
| Atrial Fibrillation or Atrial Flutter, n (%) | 15 (24.2) | 1 (2.0) | 16 (14.2) | <0.001 |
| Symptomatic, ventricular rate > 120 BPM, n (%) | 4 (6.5) | 1 (2.0) | 5 (4.4) | NS |
| Asymptomatic, ventricular rate > 150 BPM, n (%) | 12 (19.4) | 0 (0.0) | 12 (10.6) | <0.001 |
| Symptomatic bradycardia < 40 BPM, n (%) | 0 (0.0) | 0 (0.0) | 0 (0.0) | NC |
| Sustained (> 10 seconds) or symptomatic supraventricular tachycardia (> 120 BPM), n (%) | 10 (16.1) | 4 (7.8) | 14 (12.4) | NS |
| Ventricular tachycardia (> 100 BPM and > 3 beats), n (%) | 14 (22.6) | 2 (3.9) | 16 (14.2) | 0.005 |
| Any arrhythmia requiring therapeutic intervention, n (%) | 0 (0.0) | 0 (0.0) | 0 (0.0) | NC |
| Other, n (%) | 1 (1.6) | 0 (0.0) | 1 (0.9) | NS |

NC = not calculated; NS = nonsignificant.

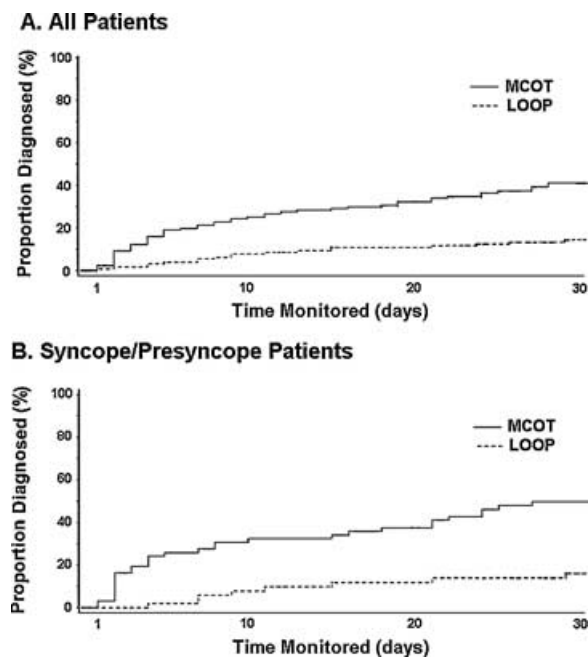


Figure 1. Cumulative proportion of subjects diagnosed with a clinically significant arrhythmia during the monitoring period in all patients (A) and in the syncope/presyncope subgroup (B) ($P < 0.05$ by Log Rank Test).

recorder patients, compared with 24% of the Holter monitor group.

To our knowledge, the present study is the largest randomized study comparing two noninvasive monitoring methods. Although the overall yield of external loop recorders was 75%, and similar to or better than previously published results,^{3,4,7-9} MCOT was shown to be significantly better in the confirmation or exclusion of a cardiac arrhythmia. Several factors may have contributed to this difference, including the ability to use the device and/or record the arrhythmia properly, patient compliance, and the detection of asymptomatic arrhythmias. In two separate studies where the proper use of loop recorders was assessed, 15% of patients were unable to send a test transmission successfully¹⁰ and 23% of patients were unable to activate the loop recorder properly at the time of their symptoms.⁸ In another study, two of 24 patients being evaluated for recurrent syncope accidentally erased a stored arrhythmia.⁵ Because MCOT provides continuous monitoring, no patient activation is necessary and some of these variables can be minimized.

Cardiac arrhythmias without associated symptoms, but nonetheless capable of causing the index symptoms, were the major determining factor accounting for the difference in yield in our study. In the MCOT cohort, 20% had a clinically significant arrhythmia that was not temporally related to any symptoms. With patient-activated monitors, asymptomatic arrhythmias will obviously be missed. To overcome this deficiency, loop recorders with an autotrigger algorithm have been used to improve the diagnostic yield. In a large retrospective review of 1,800 randomly selected records, Holter monitoring, loop recorders, and autotriggered loop recorders were assessed.¹¹ The diagnostic yield in these groups was 6%, 17%, and 36%, respectively. In a study by Balmelli et al.,¹² external loop recorders with automatic arrhythmia detection resulted in a 5-fold increase in the detection of arrhythmias. Our study was not designed to evaluate autotriggered loop

recorders, as this type of recorder was not available at all sites. A post hoc analysis of a subgroup of patients from sites that did utilize this technology, however, was performed. MCOT demonstrated a significant advantage over LOOP, with a diagnosis made in 88% of MCOT subjects compared with 46% of LOOP subjects.

In a study by Zimetbaum et al.,¹³ to determine the optimal duration of monitoring, 90% of arrhythmias were diagnosed in the first two weeks, and monitoring beyond that timeframe resulted in a marked increase in cost. In our study, the median time to diagnosis of a clinically significant arrhythmia was seven days in the MCOT group and 9 days in the LOOP groups ($P = \text{NS}$). In both groups, approximately 70% of these patients were diagnosed by the 15th day. These results are similar to other loop recorder studies where the proportion of patients diagnosed at 15 days ranged from 50% to 73%.^{7,10} Multiple factors probably account for these differences, including the frequency of symptoms, compliance with the devices, and differences in the study population. Poor compliance in wearing the monitor may result in a longer time to diagnosis, and study populations with an older age and more extensive cardiac history may have more frequent cardiac arrhythmias. A cost-effectiveness analysis of our data is ongoing.

Limitations

Since neither the investigator nor subject was blinded, a bias toward one of the monitoring modalities could occur when evaluating and categorizing the transmitted arrhythmias. We attempted to overcome this bias by having all monitoring strips and diagnoses verified by an independent electrophysiologist. Patient compliance was also a significant issue in both cohorts during our study. Withdrawal in the present study due to noncompliance was slightly more common in the MCOT group, but this may have been an artifact of reporting bias. Unmonitored periods are easily identified with MCOT, whereas with loop recorders, a patient can choose not to wear the monitor without the investigator's knowledge. We did not utilize diaries in our study to determine how often the loop recorder was worn, and it is possible that some cardiac arrhythmias were missed if patients had symptoms while not being monitored. In our study, the proportion of patients reporting symptoms (and simultaneously transmitting recordings in the LOOP group) was similar in both groups (79% in MCOT and 76% in LOOP), suggesting at least equal compliance during the early portion of the monitoring period when most transmissions and reported symptoms occurred. The inability to consistently randomize subjects to loop recorders with an autotrigger algorithm is another limitation of this study and has been discussed previously.

Conclusion

In the diagnosis of patients with symptoms of a cardiac arrhythmia, MCOT provides a significantly higher yield than standard cardiac loop recorders. This result was more pronounced in patients presenting with symptoms of syncope or presyncope. MCOT was superior to loop recorders for the detection of clinically significant arrhythmias, with a shorter time to diagnosis.

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References

1. Bass EB, Curtiss EI, Arena VC, Hanusa BH, Cecchetti A, Karpf M, Kapoor WN: The duration of Holter monitoring in patients with syncope. Is 24 hours enough? *Arch Int Med* 1990;150:1073-1078.
2. Gibson TC, Heitzman MR: Diagnostic efficacy of 24-hour electrocardiographic monitoring for syncope. *Am J Cardiol* 1984;53:1013-1017.
3. Krahn AD, Renner SM, Klein GJ, Yee R, Skanes A, Evans EM: The utility of Holter monitoring compared to loop recorders in the evaluation of syncope and presyncope. *Ann Noninvasive Electrocardiol* 2000;5:284-289.
4. Rockx MA, Hoch JS, Klein GL, Yee R, Skanes AC, Gula LJ, Krahn AD: Is ambulatory monitoring for "community-acquired" syncope economically attractive? A cost-effectiveness analysis of a randomized trial of external loop recorders versus Holter monitoring. *Am Heart J* 2005;150:e1.1065-e5.1075.
5. Schuchert A, Maas R, Kretzschmar C, Behrens G, Kratzmann I, Meinertz T: Diagnostic yield of external electrocardiographic loop recorders in patients with recurrent syncope and negative tilt table test. *Pacing Clin Electrophysiol* 2003;26:1837-1840.
6. Joshi AK, Kowey PR, Prystowsky EN, Benditt DG, Cannom DS, Pratt CM, McNamara A, Sangrigoli RM: First experience with a Mobile Cardiac Outpatient Telemetry (MCOT) system for the diagnosis and management of cardiac arrhythmia. *Am J Cardiol* 2005;95:878-881.
7. Kinlay S, Leitch JW, Neil A, Chapman BL, Hardy DB, Fletcher PJ: Cardiac event recorders yield more diagnoses and are more cost-effective than 48-hour Holter monitoring in patients with palpitations: A controlled clinical trial. *Ann Intern Med* 1996;124:16-20.
8. Sivakumaran S, Krahn AD, Klein GJ, Finan J, Yee R, Renner S, Skanes AC: A prospective randomized comparison of loop recorders versus Holter monitors in patients with syncope or presyncope. *Am J Med* 2003;115:1-5.
9. Hoefman E, Van Weert H, Reitsma JB, Koster RW, Bindels PJE: Diagnostic yield of patient-activated loop recorders for detecting heart rhythm abnormalities in general practice: A randomized clinical trial. *Fam Pract* 2005;22:478-484.
10. Gula LJ, Krahn AD, Massel D, Skanes A, Yee R, Klein GJ: External loop recorders: Determinants of diagnostic yield in patients with syncope. *Am Heart J* 2004;147:644-648.
11. Reiffel JA, Schwarzberg R, Murry M: Comparison of autotriggered memory loop recorders versus standard loop recorders versus 24-hour Holter monitors for arrhythmia detection. *Am J Cardiol* 2005;95:1055-1059.
12. Balmelli N, Naegeli B, Bertel O: Diagnostic yield of automatic and patient-triggered ambulatory cardiac event recording in the evaluation of patients with palpitations, dizziness or syncope. *Clin Cardiol* 2003;26:173-176.
13. Zimetbaum PJ, Kim KY, Josephson ME, Goldberger AL, Cohen DJ: Diagnostic yield and optimal duration of continuous-loop event monitoring for the diagnosis of palpitations. A cost-effectiveness analysis. *Ann Intern Med* 1998;128:890-895.