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REVIEW

Long-term continuous external electrocardiographic recording: a review

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Ambulatory electrocardiographic (AECG) monitoring is an essential tool in the diagnostic evaluation of patients with cardiac arrhythmias. Recent advances in solid-state technology have improved the quality of the ECG signals and new dedicated algorithms have expanded the clinical application of software-based AECG analysis systems. These advances, in addition to the availability of inexpensive large storage capacities, and very long-term continuous high-quality AECG monitoring, have opened new potential uses for AECG. New digital recorders have the capability of multichannel simultaneous recordings (from 3 to 12 leads) and for telemetred signal transduction. These possibilities will expand the traditional uses of AECG for arrhythmia detection, as arrhythmia monitoring to assess drug and device efficacies has been further defined by new studies. The analysis of transient ST-segment deviation still remains controversial, but considerably more data are now available, especially about the prognostic value of detecting asymptomatic ischaemia. Heart rate variability analysis has shown promise for predicting mortality rates in cardiac patients at high risk. We review recent advances in this field of non-invasive cardiac testing.

Introduction

In the 1940s, Dr Norman Jeff Holter (*Figure 1*) from Montana, USA, developed a 75 lb backpack that could record the ECG of the wearer and transmit the signal. His system, the 'Holter' monitor, has been greatly reduced in size, combined with tape/digital recording, and used to record ambulatory electrocardiographies (AECGs).[1,2] The recorded ECG is subsequently analysed for rhythm and ST-segment/T-wave alterations by a trained technician or physician and it currently represents an essential tool in the diagnostic evaluation of patients with cardiac arrhythmias. It is useful to recognize, characterize, and to quantify arrhythmias in patients with symptoms potentially related to an arrhythmia. The recording of a rhythm disturbance simultaneous with a patient's symptom may be the only means of diagnosis, particularly when the symptoms and arrhythmia are relatively infrequent. Today, there exist different recording techniques and many different devices on the medical market. We review recent advances in this field with regard to the technical aspects of recording and analysis and duration of recording and also review the most common indications and limitations of this widespread technique. Our review is limited to studies involving ambulatory monitoring for diagnosis of arrhythmia and directly related issues. Studies were identified through a comprehensive search of the NLM-Medline database and were selected on the basis of methodological quality and clinical relevance.

Technical aspects of AECG

AECG recording techniques

There are two general types of AECG recorders currently available: continuous recorders, typically used for 24–48 h to investigate symptoms and ECG events that are likely to occur within that time frame and intermittent or event recorders, which may be used for longer periods of time (weeks to months) to provide shorter, intermittent recordings for investigating events that occur infrequently.

Continuous recorders

The ECG can be recorded continuously on cassette tape (analogue) or digitally in solid-state memory. The tape recorder is a battery-powered, miniature device with a very slow tape speed that is small enough to be suspended by a strap over the shoulder or around the waist. The digital recording systems amplify, digitize, and store the ECG in solid-state memory. The direct digital recording avoids all of the biases introduced by the mechanical

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Figure 1 Norman Jeff Holter with one of his earlier AECG recorders.

features of tape recording devices and the problems associated with recording data in an analogue format, which requires analogue-to-digital conversion before analysis with a personal computer. With a digital recorder, ECG signals can be recorded at up to ~1000 samples per second, which allows extremely accurate reproduction of the ECG signal. This accuracy is necessary to perform signal averaging and other sophisticated ECG analyses. In contrast to cassette tape recorders, current digital recorders give much greater quality of ECG signal, with a more favourable noise-to-signal ratio, and provide full disclosure with accurate reconstruction of the waveforms with minimal loss of information. Current recorders can now record 3–12 simultaneous leads, allowing the reconstruction of standard 12 leads for 24–48 h. The solid-state recorders are able to analyse the signal immediately and rapidly ('on-line analysis'), and use this to optimize the signal quality and provide immediate feedback to the patient.

Nonetheless, digital recorders have some limitations, as the recordings are less easy to archive and to exchange among different centres for reasons of incompatibility. To overcome the latter problem, the International Society of Holter and Non-invasive Electrocardiology (ISHNE) established in 1997 a standard 'output' format (IHF, 'ISHNE' Holter Format), which is now implemented in the most modern Holter equipment, allowing the exchange of raw digital Holter files among different Holter systems. As this format is secondary, it does not require the 'disclosure' of the compression and interpolation algorithms of the manufacturers.[3]

Intermittent recorders

An alternative method is not to record continuously, but only when the patient senses symptoms or an event. These recorders often use solid-state memory and can transfer data readily over conventional telephone lines. They can also be used for long periods of time (weeks to months) to identify infrequently occurring arrhythmias or symptoms that would not be detected with the use of a conventional 24-h AECG recording. On the basis of the type of memory, there are two types of intermittent recorders that have slightly different utility.

Event recorders (*post-event recorders*) store only a brief period of ECG when activated by the patient in response to symptoms. It may monitor the ECG via attached leads or the patient wears it in a pocket and places it on the precordium if symptoms occur. Some new devices are credit card size, to be carried in a wallet, or worn as a necklace or wristwatch. The recorded data are stored in memory until the patient submits the information directly or transtelephonically to an ECG receiver, where it is recorded. Event recorders can usually memorize only a few minutes of ECG, but they can be programmed to acquire multiple events. Event recording is also provided by new-generation pacemakers and implantable cardioverter defibrillators (ICDs). These devices recognize abnormal rhythms, such as tachycardia, and provide, via telemetric transmission, either actual ECG records or an analysis of the number, rate, and duration of recognized arrhythmias. Another variation is real-time monitoring, where the device that acquires the data can transmit them directly and transtelephonically in real-time without recording the data in the device.

Loop recorders (*pre-event recorders*) record the ECG in a continuous manner but store only a brief period of ECG recording. The rhythm is monitored continuously via leads either at the extremities or over the precordium, connected to a recorder typically worn on a belt. Patients activate the unit in response to symptoms, so that an abnormal rhythm or an ECG synchronous with the symptoms can be recorded. The number of events that can be recorded and the allotment of recording time prior to and after activation of the unit are programmable. Newer miniaturized loop recorders can be implanted subcutaneously for very long-term monitoring.[4] The size is smaller than that of a typical pacemaker. The battery power lasts approximately 18–24 months and they record a single channel ECG continuously by electrodes that are built into the recorder itself. The overall recording time is up to 42 min. The recording time is usually a few minutes per event and the recorder can store multiple events. The patient can activate the device, if symptoms occur, or the device can be programmed to record the ECG on a pre-specified basis. The recorder is usually programmed to detect bradyarrhythmias and tachyarrhythmias automatically through the detection of cycle lengths outside programmed limits, and asystole of more than 3 or 4 s. The recorded electrogram data can be gathered by telemetry, to a pacemaker programmer. The advantage of this system is the very long-term monitoring period, allowing the identification of infrequent events, such as syncope.[5] However, these systems require subcutaneous implantation and are relatively expensive.

Data analysis techniques

The ECG recording can be analysed by scanning the tape or digital record at high speed after the recording has been made ('off-line'), by printing it out directly or by processing it during the recording ('on-line') and printing out the analysis at the end of sampling. Most current analysis systems use generic personal computer hardware platforms, run proprietary software for data analysis, and report generation. Such systems provide the time-tested scanning techniques of visual superimposition, an RR histogram, full-disclosure paging, template matching, and full operator interaction to provide accurate analysis of the recorded ECG.

A commonly used method is the operator-dependent analysis, in which a trained technician or physician interprets the played back ECG on a monitor at 30–240 times the speed of the record. Through superimposition of each QRS complex on the immediately preceding complex, identical QRS complexes present as stationary image on the monitor (audio-visual superimposition ECG presentation, AVSEP). Variations in QRS morphology then become rapidly apparent. The RR histogram displays a graphical bar that is proportional to the length of the RR interval. Combined with an audio signal and colour coding for premature beats, the operator can easily note an abnormal event and then can slow the playback to normal speed to permit detailed analysis of the ECG either by full-disclosure paging or print out to paper. The newer method of template matching allows definition of the patient's own QRS complexes and programming of the analysis unit so that it can recognize any deviation from normal, providing clusters of subsequent beats according to their morphology and classify their accuracy. The automatic classification provided by the system can later be overviewed and modified by the operator, to finalize the clinical validation of the automatic arrhythmia analysis. The computer can provide summaries of heart rates, frequency of premature supraventricular or ventricular beats, runs of tachycardia or other arrhythmias, and variations in QRS, ST, QT, or T-wave patterns during any time period.

Arrhythmia monitoring

Operator-dependent high-speed AVSEP analysis of the AECG performed by a trained physician usually recognizes serious rhythm disturbances. On the other hand, even a skilled operator may sometimes fail to recognize arrhythmias using this method.[6] Electronic analysis systems improve the sensitivity and specifity of interpretation of the AECG recordings. The technique used for this analysis by different manufacturers is usually not disclosed in detail for competitive reasons. Thus there are only a few papers comparing different analysis systems head-to-head. However, the positive predictive accuracy depends on the type of ectopy or arrhythmia sought,[7] and varies in one study by von Leitner *et al.*[8] between 46% for asystole and 97% for premature ventricular complexes (PVCs). More recent studies conducted by different authors showed similar results (*Table 1*). Computer-analysis systems are somewhat better in detecting PVC than premature supraventricular complexes (PAC). This depends on their ability to detect the wider QRS complex of PVC and the ability to build different clusters for comparison, whereas the PAC detection mostly depends on the preset prematurity. The prematurity can be modified by the operator, which makes the analysis more precise. A computer-analysis system cannot accurately diagnose supraventricular ectopy with aberrancy or intermittent pre-excitation. Even in well-run laboratories, intra- and interobserver variabilities may lead to discrepancies of 10–25% in total ventricular arrhythmia estimations for the same recording, if frequent or complex arrhythmias are present.[9] In conclusion, the accuracy of arrhythmia diagnosis is questionable when the data are not fully disclosed.

A more recently published study tested the reliability of computer-assisted AECG analysis of pacemaker malfunction in patients with ventricular demand pacemakers.[10] In this study, Brandes *et al.*[10] found in 100 patients with permanent ventricular inhibited demand pacemakers, a positive predictive value that was limited to 60% for detection of failures to sense and 63% in detecting inappropriate inhibitions. The overall positive predictive accuracy was 60%. They concluded that visual control and validation by an experienced physician is mandatory. Almost no data are available

Table 1 Sensitivity and positive predictive accuracy for different arrhythmias and different analysis systems

Arrhythmia	Author, reference	Patients (*n*)	Sensitivity (%)	Positive predictive accuracy (%)	False positive
PVC	Leitner[8]	37	95.3	97.2	
	Lanza[118]	152	92.9	94.9	
	Kennedy[119]	164	92	92	8
	Cooper[120]	50	96	99	0.9
PVC couplets	Leitner[8]	37	93.4[a]	91.8[a]	
	Lanza[118]	152	90.1	87.8	
	Kennedy[119]	164	80	97	3
	Cooper[120]	50	92	92	7
VT	Leitner[8]	37	93.4[b]	91.8[b]	
	Lanza[118]	152	80	82.3	
	Kennedy[119]	164	81	92	8
	Cooper[120]	50	86	90	10
More than three PVC	Leitner[8]	37	97.4	82.1	
	Lanza[118]	152	88.6	56.6	
	Kennedy[119]	164	81	82	18
SVT	Lanza[118]	152	43.7	60.2	
	Kennedy[119]	164	75	89	11

VT, ventricular tachycardia; SVT, supraventricular tachycardia.
[a]Including VT.
[b]Including PVC couplets.

regarding the head-to-head comparison between different analysis techniques of AECG to detect arrhythmias.

Ischaemia monitoring

AECG to detect ST-segment changes was first introduced into clinical practice in 1974.[11] Although initially there was much scepticism about its validity, and still not all technical problems have been resolved, improvements in technology have increased interest in the use of this method.

Questions about the meaning of ST-segment changes during AECG, particularly of those changes unaccompanied by anginal symptoms, have been answered to some degree by their high degree of correlation with simultaneous positron emission tomography[12] and myocardial function.[13] Although these studies were conducted only in small groups of patients with known coronary artery disease (CAD), they suggest that the ST-segment changes often represent actual ischaemic episodes. Interpretations of ST-segment changes recorded during AECG monitoring are subject to the same limitations as interpretations of such changes on an exercise treadmill test. Causes of false positive tests include medications, electrolyte abnormalities, hyperventilation, posture changes, and lead placement. To optimize recordings of the low-frequency (LF) ST-segment, skin resistance may be measured with an impedancemeter once the electrodes are applied and the measured resistance should be $\leq 5\,k\Omega$, preferably $\leq 2\,k\Omega$. In a recent study, Lanza *et al.*[14] compared simultaneous recordings of a conventional 12-lead ECG recording during an exercise treadmill test with a three-lead AECG recording. The authors found that the standard lead C_5 had the highest sensitivity (89%) in detecting myocardial ischaemia. The addition of lead C_3 increased the sensitivity to 91%, and the addition of an inferior lead to C_5 increased the sensitivity to 94%, particularly improving the sensitivity of isolated inferior ischaemia. The combination of all the three AECG leads had a sensitivity of 96%, only 2% more than the best combination of the best two leads (C_5 plus an inferior lead). Some new AECG monitor systems can record a 12-lead ECG, whereas other systems derive a 12-lead ECG from the three-lead data through the use of a mathematical transformation. To date, no data are available regarding a comparison between these two methods in the detection of ischaemia. Another technical problem is the instability of the isoelectric line, which is a greater problem in the analysis of the ST-segment, than in arrhythmia analysis. The QRS-T morphology must be carefully scrutinized to ensure that it is suitable for interpretation to identify ischaemic changes.[15]

Heart rate variability

The variability of RR intervals between two normal beats (normal-to-normal interval, NN) gives important information about the autonomic control of the heart rate.[16] There are two broad classes of techniques for investigating heart rate variability (HRV): time-domain and frequency-domain techniques. With time-domain techniques, HRV can be quantified in terms of changes in mean heart rate or RR interval during a Holter recording or in response to interventions such a Valsalva manoeuvre or body posturing. Frequency domain techniques are particularly useful for the analysis of short-term recordings (min).[17] Parametric (autoregression) or non-parametric (fast Fourier transformation) techniques may be applied to the data to examine the oscillatory behaviour of heart period. Both techniques produce a power spectral density of the RR intervals. Power spectral measures of the RR time series can delineate cyclic fluctuations in the RR intervals in terms of their frequency and amplitude. Physiological perturbations and pharmacological interventions help to define physiological systems responsible for cyclic fluctuations in RR intervals. When applied to short ($\sim$5 min) recordings, frequencies between 0.033 and 0.4 Hz can be evaluated. In a healthy subject, three prominent peaks are apparent, in the supine position: a high-frequency (HF) peak between 0.15 and 0.4 Hz, a larger LF peak between 0.04 and 0.15 Hz, and an even larger very low-frequency (VLF) peak between 0.033 and 0.04 Hz. The HF peak represents a pure vagal efferent signal that is modulated by ventilation (respiratory sinus arrhythmia). LF power has contributions from vagal and sympathetic modulations of RR intervals. For these reasons HF and LF power can provide important information about the autonomic nervous system. The LF to HF power ratio has, therefore, been used as an index of vagosympathetic balance. The power of these spectra may be expressed either in absolute units or as a proportion of total power (normalized units).[17] The analysis techniques are commercially available together with a Holter analysis system.

Variability of arrhythmias and optimal duration of recording

When AECG is used to detect arrhythmias during symptoms, simply prolonging the duration of recording, either by using a continuous recording system or an event recorder, until the symptom occurs, will compensate for day-to-day variability. Hence, knowledge about the day-to-day variability of arrhythmias is essential when AECG is used to guide antiarrhythmic therapy or to estimate prognosis.

Variability in the results may be due to several factors. One factor is the intra- and interobserver variabilities of 10–25% in ventricular arrhythmia estimations for the same recording that leads to some degree of variability.[9] To minimize this type of variability, AECG-laboratories should routinely monitor their own accuracy; different libraries of standard AECG recordings exist for blind analysis of arrhythmias[18] and analysis of the ST-segment.[19] There are some studies that investigated the day-to-day variability of arrhythmias in selected patients with CAD, cardiomyopathy, or mixed diagnoses. In summary, the estimates of percent reduction in arrhythmia frequency after an intervention that ensures that the change was an effect of the treatment for PVC ranged from 63 to 95%.[20] Almost no data exist on the day-to-day variability of PAC. Most arrhythmia studies use a 24-h period, although yield may be increased slightly with longer recordings or repeated recordings, especially in patients with unexplained syncope and concomitant diseases.[21]

Variability of ischaemic episodes and optimal duration of recording

There is a well-known variability of the frequency, duration, and depth of ischaemic ST-segment depression. Nabel *et al.*[22] analysed 4656 h of AECG recordings acquired in 42 patients with known CAD. The number of episodes was $6.3 \pm 0.5/24$ h, and the duration of episodes was

18.3 ± 2.8/24 h. Other studies found a high day-to-day variability, as well.[12,23] Tzivoni *et al.*[23] found that the day-to-day variability in individual patients between the different days in the number of ischaemic episodes was 36%, in duration 51%, and in maximal degree of ST-depression 31%. Because many ischaemic episodes in daily activity are related to a change in heart rate due to physical or emotional activities, it is necessary to encourage patients to document daily activities during an AECG recording. However, the optimal duration of recording to detect and quantify ischaemic episodes is ≥48 h.[23]

AECG monitoring in patients with symptoms possibly related to arrhythmia

Palpitations

AECG was originally intended to provide a tool to assess the cardiac rhythm during daily activities. However, many arrhythmias are non-sustained and may occur without obvious immediate provocation and at unpredictable intervals. Unexplained recurrent palpitations are, therefore, a widely accepted indication for AECG (ACC/AHA Guidelines Class I).[24] If arrhythmias are thought to be causative in patients with palpitations, the crucial information needed is an ECG recording at the precise time that the symptom is occurring. The characteristics of the symptoms will often determine the choice of the recording techniques (*Table 2*). Continuous recorders are particularly useful if symptoms occur daily or almost daily, although for most patients episodic symptoms are infrequent. Such a recording should include a patient diary of symptoms and concurrent activities and the use of an event marker that is built into the recorder. The event marker is activated whenever the patient has typical symptoms, simplifying the identification of the point in time during the recording when symptoms occur. For less frequent symptoms (weekly or monthly), an intermittent recorder is more useful. For selected patients with a high probability of significant and severe arrhythmias, the subcutaneous implantation of a loop recorder (Reveal® Plus Medtronic, Minneapolis, MN, USA) may be indicated. Palpitation accounts for 31–43% of indications for AECG recordings.[25,26] Only few studies have assessed the diagnostic yield of Holter monitoring and/or event recording for palpitations.[27–31] Taking the data from the studies together with those data reviewed by Zimetbaum and Josephson,[32] it is now established that the diagnostic yield for palpitations from Holter monitoring is about 35%. This diagnostic yield can be roughly doubled by the use of a transtelephonic event recorder, and these devices are more cost-effective for this indication than Holter monitoring.[33,34] The latter two recent studies are in line with a study by Zimetbaum *et al.*[34] who addressed the issue of the duration of recording with the transtelephonic event recorder. The authors conclude that a monitoring period of 2 weeks is sufficient to make a diagnosis in the vast majority of patients with palpitations.

Syncope

Syncope is a very prevalent disorder in the general population.[35,36] As in patients with palpitations, the pre-test likelihood of a serious arrhythmic cause of syncope is substantially increased in patients with underlying heart disease. Kapoor[37] reported a 5-year mortality of 51% in patients with a cardiac cause of syncope that was significantly higher than the 30% mortality in patients with a non-cardiac cause or 24% in patients with an unknown cause: a cardiac cause of syncope was an independent predictor of sudden death and mortality. In the ACC/AHA Guidelines, AECG is a Class I indication for patients with unexplained syncope, near syncope, or those with episodic dizziness in whom the cause is not obvious.[24] Unfortunately, the yield of AECG monitoring for syncope, near syncope, or dizziness is relatively low. In a review of seven retrospective studies of Holter monitoring for syncope before 1990, DiMarco and Philbrick[20] found a direct relation between symptoms and syncope in only 22% of patients. A more recent prospective study found a diagnostic yield of 25%,[38] three retrospective studies of transtelephonic monitors reported diagnostic yields from 6 to

Table 2 Types of recorder for specific indications and duration of recording

	Type of recorder	Duration of recording	Diagnostic yield (%)
Palpitations	Intermittent recorder[a]	During symptoms, up to 4 weeks	∼35
Syncope/presyncope	Intermittent recorder	Depending on frequency of event[b]	∼31–58
Atrial fibrillation and cerebrovascular events[c]	Intermittent recorder		Low diagnostic yield, not routinely recommended
Ischaemic episodes	Continuous recorder or intermittent recorder	>48–96 h	∼27–94[d]
Prognosis of myocardial infarction	Continuous recorder for HRT—analysis	HRT—analysis[e]	
Drug therapy[f]	Continuous recorder	24–48 h	

[a]Depending on frequency of symptoms, intermittent recorders should be used; if symptoms occur on a daily basis, continuous monitoring could be used as well.

[b]Intermittent recording with a duration of recording up to 24 month with an implantable recorder possible.

[c]Because of low diagnostic yield, Holter monitoring is not routinely recommended for initial work up. History taking, physical examination, 12 lead ECG, etc. should be used (ACC/AHA Guideline Class IIb indication).

[d]Diagnostic yield highly depends on length of recording.

[e]Prognosis after myocardial infarction depends on several parameters (left ventricular function, heart rate turbulence (HRT), etc.) For HRT — analysis, at least five PVC are needed; most studies are done by continuous recording.

[f]Indication only established to monitor patients with atrial fibrillation who receive drugs for rate control.

31%.[39–41] There may be a problem of the definition of syncope in these studies, because the diagnostic yield for pre-syncope in these analyses was 36–59%.[40,41] These findings are in line with a more recent study by Wu *et al.*[28] who found a diagnostic yield for pre-syncope of 57%. A study by Sivakumaran *et al.*[42] compared Holter monitors with loop recorders in a prospective randomized cross-over design. One hundred patients with syncope or pre-syncope were randomized to either a 48-h Holter monitor or a loop recorder for 1 month and if the initial approach failed, they were offered the use of the other system for diagnosis. The authors found an overall probability to obtain a symptom–rhythm correlation of 56% for loop recorders vs. 22% for Holter monitors ($P < 0.0001$). However, a common problem of the loop recorder was a failure to activate the loop recorder properly in 23% of the patients who had recurrence of their symptoms. In selected patients, the use of an implantable loop recorder can lead to a diagnostic yield of 52–58% for the diagnosis of syncope.[43,44] These data suggest, that the preferred diagnostic tool for diagnosis of an arrhythmogenic cause of syncope or pre-syncope is the loop recorder (*Table 2*).

Atrial fibrillation and cerebrovascular events

Paroxysmal atrial fibrillation (AF) is an important cause of cardiogenic cerebral embolism, which leads to stroke or transient ischaemic attack. The prevalence is probably greatly underestimated, as data from Holter monitoring suggest that many AF episodes are asymptomatic.[45] In patients aged $\geq$70 with AF, symptomatic cerebral infarctions are 2.4 times more common than in AF-free controls.[46] However, the diagnostic yield of AECG for AF is low. The studies published between 1982 and 1996, investigating the incidence of AF in stroke patients[47–52] included small numbers of patients. AF incidence was between 3[47] and 24%, with an average of 8% (62 of 817).[52] Moreover, in two of these studies including 250 patients, AF was known by history or 12-lead ECG in 14 of 15 AF patients,[49,51] indicating an even lower incidence. In a more recent retrospective study conducted by Schaer *et al.*, the investigators found that of the 425 24-h recordings, only 21 patients had AF.[53] In 12 patients, AF was permanent or persistent and the diagnosis was already established by history or 12-lead ECG. Only in nine patients was AF established as a new diagnosis. In another recent study including 60 patients with cerebrovascular events, 28 patients with negative routine work-up including a Holter-ECG, were examined with an event recorder for a mean duration of 70 $\pm$ 39 h. In 14% of patients, sustained ($\geq$30 s.) AF was found.[53] Because of the low diagnostic yield of routine Holter monitoring for AF in patients with neurological events in whom AF or atrial flutter is suspected, Holter monitoring is considered an ACC/AHA Guideline Class IIb indication (*Table 2*).[24] For patients with cerebrovascular accidents without evidence of arrhythmia, Holter monitoring is an ACC/AHA Guideline Class III indication.[24]

AECG monitoring for myocardial ischaemia

Since the initial proposal of the use of AECG monitoring to detect ST-segment changes in 1974,[11] this technique has always been questioned. However, technological advances in the past decades made it possible that ST-segment analysis provides accurate and clinically meaningful information about myocardial ischaemia in patients with CAD. Numerous studies have evaluated the prevalence and prognostic impact of myocardial ischaemia by AECG in patients with proven CAD.[54–63] In these studies, the prevalence ranged from 18 to 87%. The reason for the variability in the prevalence may be due to the medication used during the recording or its duration. In some studies, patients were monitored off medication for the control of symptoms. Unfortunately, data regarding the role of AECG monitoring in asymptomatic patients without known CAD are missing. Unlike exercise testing, AECG monitoring has the advantage of providing long-term monitoring for myocardial ischaemia in the outpatient setting while the patient is performing usual daily activities.[64,65] In a study by Mulcahy *et al.*[64] 277 patients with proven CAD and stable angina were studied with treadmill testing and 48 h Holter monitoring. The investigators found, during 11 964 h of recording, 881 episodes of ischaemia. A total of 73% of the episodes were silent and 92% of the episodes occurred in patients with a positive exercise test.[64] During recent years, AECG has been used for the evaluation of efficacy of anti-ischaemic therapy in patients with CAD. In another study, with 96 h recordings registered with an intermittent recorder (R-Test) in 1022 patients with CAD, the investigators found ischaemic events in 27% of the patients and among these events, 55% were silent.[66] Among the silent episodes, only 64% were registered during the first 24 h. This increased to 83% after 48 h and 94% after 72 h. This study pointed out the importance of the length of recording in the detection of myocardial ischaemia (*Table 2*). A number of studies have demonstrated that 48-h AECG monitoring at baseline and after institution of therapy can provide reliable data about the efficacy of anti-ischaemic medication in patients with CAD.[67–76] However, whether these results have an impact on prognosis in patients with CAD needs to be confirmed by large-scale, prospective, randomized trials. For these reasons, AECG monitoring of patients suspected to have variant angina is an ACC/AHA Guideline Class IIa indication.[24] The AECG evaluation of patients (with chest pain or scheduled for vascular surgery) who cannot exercise is an ACC/AHA Guideline Class IIb indication.[24] When interpreting data provided by ST-segment analysis, it is necessary to be aware that there are other possibilities than ischaemia for ST-segment changes. These include hyperventilation, hypertension, LV-hypertrophy, LV-dysfunction, conduction abnormalities, and other clinical conditions. Because of the complex technical requirements and diagnostic criteria mentioned earlier, it is necessary to have highly trained staff and a well-equipped laboratory.

AECG monitoring in assessing prognosis

AECG monitoring is used to assess prognosis in patients with and without symptoms of arrhythmia and underlying diseases. In this review, we have confined our attention to the common cardiac diseases: myocardial infarction (MI), congestive heart failure, and hypertrophic cardiomyopathy (HCM) (*Table 2*).

Myocardial infarction

Since the introduction of beta-blockers and antithrombotic therapy into clinical practice, epidemiological data suggest a change in the common arrhythmia risk variables.[77] In

post-MI patients, the major causes of sudden death are ventricular tachycardia and ventricular fibrillation with the highest incidence within the first year after the cardiac event.[78,79] Owing to the increased use of thrombolytic agents and urgent coronary revascularization, the current 1-year risk of developing a malignant arrhythmia after a MI after hospital discharge is $\leq$5%.[80,81] AECG has been suggested as a non-invasive test to assess prognosis in these patients.

In most studies, AECG is performed between 6 and 10 days after acute MI. Because the association between ventricular events and adverse cardiac events has been demonstrated previously,[82] repetitive PVC and VT are of greatest interest. The positive predictive value of ventricular ectopy ($\geq$10 PVC/h, non-sustained VT) in most studies for arrhythmogenic events is low and ranges from 5 to 15%.[24] The sensitivity can be increased by the combination with other measures of prognosis, e.g. ejection fraction (EF). The positive predictive value for an arrhythmic event increases to 15–34% if combined with EF.[78,83,84]

The assessment of HRV has become an important clinical technique for risk stratification after MI. The predictive value of HRV in patients following MI was first suggested by Wolf *et al.*,[85] who demonstrated that patients with MI who lacked sinus arrhythmia on admission had a higher risk of in-hospital mortality. The predictive value, however, was first recognized by Kleiger *et al.*[86] who investigated HRV in 808 survivors of MI. The finding that low values for HF measures of HRV and baroreflex sensitivity indicate decreased vagal modulation of RR intervals and are independent predictors of increased mortality in patients after MI, was also confirmed by other investigators.[87–91] Subsequently, numerous studies explored the prognostic value of HRV parameters for predicting the outcomes in post-infarction patients.[86,91–94] They consistently indicate that depressed HRV is associated with all-cause and cardiac mortality. However, there are conflicting data regarding the prognostic significance of HRV parameters for predicting sudden or arrhythmic death. Nolan *et al.*[93] studied HRV parameters in 433 CHF patients enrolled in the UK Heart study, in which they also found a significant association between time-domain parameters of HRV and all-cause mortality and mortality from progressive heart failure. However, HRV parameters were not predictive for sudden cardiac death (SCD) in this population, although in studies by Fauchier[94] and by Brouwer,[95] a significant association between depressed HRV and SCD was demonstrated. The paucity of clear evidence for the association between depressed HRV parameters and SCD might be because of the difficulty in categorizing the sudden or arrhythmic nature of death, but also could be due to lack of strong evidence for this association. This might be, in part, explained by the findings of Duru *et al.*,[96] who demonstrated a significant decrease in time- and frequency-domain measures in a control group of patient with CAD and impaired left ventricular function, suggesting an ongoing process of sympathovagal imbalance in favour of sympathetic dominance. However, the predictive value of HRV alone is only modest. The positive predictive value in most studies ranged between 10 and 48%.[86–91] Combination of HRV with other predictive factors yields better positive predictive accuracy.

In 1999, Schmidt *et al.*[97] published a new method for risk stratification, named 'heart rate turbulence (HRT)'. They investigated short-term fluctuations of sinus-rhythm cycle length after a single ventricular premature beat recorded in Holter electrocardiograms, and characterized the fluctuations by two numerical parameters, termed turbulence onset and turbulence slope (TS). In low-risk patients, sinus rhythm exhibits a characteristic discharge pattern composed of an early acceleration and a subsequent deceleration. In post-MI patients at high risk of subsequent death, HRT is blunted or abolished.[98] The exact physiological mechanisms of HRT are not fully identified, but it is believed that it is caused by a baroreflex mechanism.[98] The method has been validated in three study populations: the Multicenter Post-Infarction Program (MPIP),[79] European Myocardial Infarction Amiodarone Trial (EMIAT),[99] and the Autonomic Tone and Reflexes After Myocardial Infarction Study (ATRAMI).[89] In all three populations, the parameters of HRT were strong predictors of mortality.[98] In a study by Barthel *et al.*,[100] of the 1455 survivors of MI, with a primary endpoint of all-cause mortality, 70 patients (4.8%) died. Multivariate analysis again showed that a combination of abnormal measures of HRT was the most powerful risk stratifier [relative risk 5.9, 95% confidence interval (CI) 2.9–12.2], followed by EF $\leq$30% (relative risk 4.5, CI 2.6–7.8), diabetes mellitus (relative risk 2.5, CI 1.6–4.1), and age $\geq$65 (relative risk 2.4, CI 1.5–3.9). This study found that in patients with EF $\leq$30%, having abnormal values of HRT variables indicated a nearly 40% 2-year mortality rate, and that patients who had EF $>$30% were still at high risk, if they were diabetic, were older than 65 years, and had a single abnormal HRT parameter. The receiver operating characteristic (ROC) curves from this study for HRT, EF, and the SDNN parameter of HRV are shown in *Figure 2*.[101] The ROC curves show the tradeoff between sensitivity and specificity that occurs with choice of cutoff values. A test is considered to be highly discriminant when the area under the ROC curve is

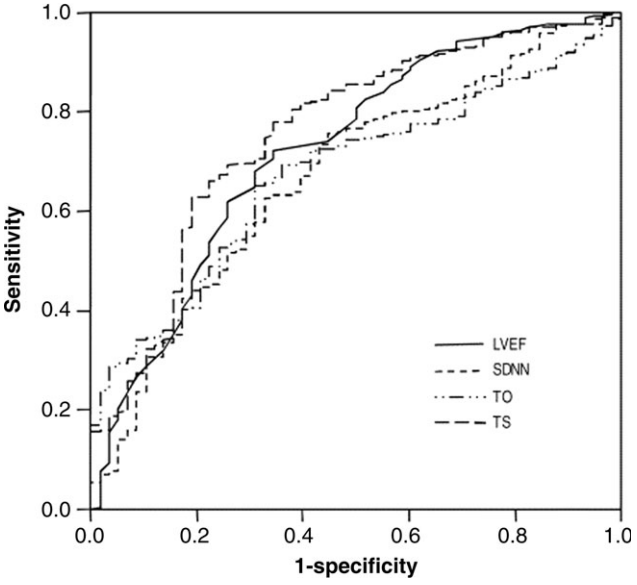

Figure 2 ROC curves from 1031 patients reported by Barthel *et al.*[100] The areas under the curves were: turbulence slope (TS) 0.76, left ventricular ejection fraction (LVEF) 0.72, turbulence onset (TO) 0.68, and SDNN parameter of heart rate variability 0.67. The ROC curve shows the tradeoff between sensitivity and specificity that occurs with choice of cutoff values. A test is considered to be highly discriminant when the area under the ROC curve is close to 1 and not discriminant if the area is close to 0.5. Figure modified from Watanabe *et al.*[101]

close to 1 and not discriminant if the area is close to 0.5. The curve for TS was highest over most of the range and consequently had the greatest area below it of 0.76, compared with an area of 0.72 for EF. Three more recent studies investigated HRT in the peri-MI setting. The study by Bonnemeier *et al.*[102] demonstrated a close relationship between TIMI-flow and HRT in the peri-MI patient. They measured HRT before and after percutaneous coronary intervention and found that HRT improved after establishing TIMI-flow III, but failed to show an improvement in HRT after establishing TIMI-flow II. Another important study in this field found a strong relation of HRT and long-term mortality in the first 24 h after MI (hazard ratio 6.9).[103] This study underlines the importance of early risk assessment after MI, as the first studies found only a weak association of HRT and MI as they recorded Holters taken 1–2 weeks after MI. These data are in line with a study done by Jokinen *et al.*[104] who found a decreasing prognostic significance of HRT 1 year after MI. These data together with the findings in patients with non-ischaemic heart disease further support the concept of HRT as a valuable non-invasive and inexpensive test. Prospective, large-scale trials are, however, needed to answer the question whether the sensitivity and positive predictive accuracy of HRT can be improved by development of age-, pathology-, or heart rate-based formulae that define normal ranges of HRT. Furthermore, more basic science research is warranted to delineate the underlying mechanisms of HRT.[101]

Congestive heart failure

Patients with congestive heart failure with underlying cardiomyopathy, whether of ischaemic or non-ischaemic origin, have an increased risk of sudden death.[105–108] However, there are conflicting data regarding the use of Holter monitoring for this group of patients. Data from three small, early trials could show that patients with mixed causes[109] of congestive heart failure and idiopathic dilated cardiomyopathy[110,111] have a higher prevalence of ventricular arrhythmia and a high mortality. A retrospective study in a larger cohort of patients with idiopathic dilated cardiomyopathy found that the prevalence of non-sustained VT on Holter monitoring is an independent arrhythmia risk factor.[112] However, the same research group failed to validate these data in their prospective trial involving 343 patients with idiopathic dilated cardiomyopathy. During the 52 $\pm$ 21-month follow-up, only left ventricular function turned out to be a significant arrhythmia predictor.[113] However, non-sustained VT was associated with a trend to a higher arrhythmia risk.[113] In a study conducted by Singh *et al.*[114] involving 674 patients, the investigators found a prevalence of 80% for non-sustained VT in patients with ischaemic cardiomyopathy. Non-sustained VT was not an independent predictor for all-cause mortality or sudden death in that population.[114] Two studies of dilated cardiomyopathy found that HRT was significantly reduced, suggesting a worse prognosis.[115,116] However, there is insufficient evidence to support the use of routine AECG for non-invasive risk stratification in patients with CHF regardless of the aetiology (ACC/AHA Guideline Class IIb, *Table 2*).[24]

Hypertrophic cardiomyopathy (HCM)

Sudden death and syncope are common in patients with HCM. One study in 99 patients with HCM found that patients with ventricular tachycardia on Holter monitoring are at a higher risk for sudden death (annual mortality rate 8.6%).[117] Another study with 86 patients with HCM found comparable results.[118] A more recent study conducted by Fananapazir *et al.*[119] investigated the use of clinical, Holter, cardiac catheterization and electrophysiological variables in 230 patients with HCM. The investigators found that VT on Holter monitoring in patients without impaired consciousness is of benign prognostic significance, sustained VT induced by electrophysiological testing identifies patients of high risk for cardiac events.[119] In another prospective evaluation of 151 asymptomatic patients with HCM and non-sustained VT, there was no increased risk of mortality associated with this arrhythmia.[120] Cecchi *et al.*[121] found in their prospective study of 167 consecutive unselected patients with HCM and frequent bursts of VT, no impact on prognosis during a mean follow-up of 10 years. In the study of Monserrat *et al.*,[122] non-sustained VT proved to be an independent risk factor for sudden death in patients $<$30 years of age. However, the investigators did not find a relation between the duration, frequency, or rate of non-sustained VT runs and prognosis at any age.[122] These studies are in line with another study showing that HRT is not a risk predictor in patients with HCM.[123] Clinically, the history of syncope and the family history are important prognostic factors, and every patient should be evaluated in this regard. Taken together, these studies suggest that Holter monitoring alone is not sufficient for risk assessment in adult patients with HCM, making it an ACC/AHA Guideline Class IIb indication for risk assessment (*Table 2*).

AECG monitoring to assess antiarrhythmic drug efficacy

The limitations of antiarrhythmic medications are the possibility of the recurrence of the primary arrhythmia and the development of a secondary arrhythmia, putting patients at risk for bradycardia-related syncope or tachycardia-related sudden death. The risk of events through proarrhythmic effects of antiarrhythmic medications is closely related to the underlying medical condition (e.g., CAD, congestive heart failure) and the dosage of the drug. AECG has been widely used to assess the efficacy of antiarrhythmic treatment, but the AECG is limited by a high day-to-day variability of the frequency and type of arrhythmia and the lack of correlation between arrhythmia suppression by medical therapy and the patient outcome. The Cardiac Arrhythmia Suppression Trial (CAST) tested the hypothesis that suppression of spontaneous ectopic beats by antiarrhythmic drugs would reduce mortality rates in patients with asymptomatic arrhythmias.[124–126] Because of the increased mortality due to arrhythmia and acute MI complicated by shock in the active treatment arm (flecainide or encainide) of CAST, the suppression of ventricular ectopy with a Class I antiarrhythmic drug is no longer recommended as long-term therapy. This changed the indications for AECG monitoring to assess antiarrhythmic drug efficacy. Now, the most accepted indication for Holter monitoring of patients to assess efficacy of drug therapy is to check rate control in patients with AF (*Table 2*).

AECG monitoring to assess device function

AECG is a useful tool in the assessment of patients suspected of significant arrhythmias and can help to establish

a diagnosis, leading to the implantation of a pacemaker or an ICD. Once a device is implanted, Holter monitoring may be helpful in assessing post-operative function as well as guiding appropriate programming of the device, such as rate response features or to document and fully characterize mode switch episodes. As new generation pacemakers and ICDs have the ability to store and analyse ECGs post-implantation, Holter monitoring is now a very rare indication. Furthermore, some devices can be programmed to record ECGs like loop recorders. These data can be retrieved during the regular follow-up visits. The resolution of the ECGs, however, is usually not high enough to allow more sophisticated analysis. Another limitation is that under-sensing or oversensing of events that occur during blanking periods may lead to false counting of events. Newer ICDs and pacemakers have the ability to record more detailed ECGs during longer periods of time, and are more comparable with loop recorders. AECG is useful for the follow-up of patients with symptoms that may be related to a pacemaker or ICD such as palpitations, syncope, or near syncope occurring as a result of pacemaker inhibition by oversensing or detection of pacemaker-induced tachycardia (ACC/AHA Guideline Class I).[24] Another Class I indication is suspected component failure or malfunction when the interrogated data are not sufficient to establish a diagnosis.[24] AECG can also be used to guide antiarrhythmic therapy after ICD implantation to reduce the episodes of ICD discharge.[24]

AECG monitoring in selected populations

Epilepsy

Patients with epilepsy have an increased risk of dying suddenly and without explanation, a phenomenon called sudden unexplained death in epilepsy (SUDEP). The underlying pathophysiology of SUDEP is unclear. Cardiac arrhythmias, central apnoea, and neurogenic pulmonary oedema have been postulated in both clinical and experimental studies. Recently, a study by Rugg-Gunn *et al.*[127] focused on centrally-mediated cardiac arrhythmias, as disturbances in heart rate have been reported in various cerebral conditions, including epilepsy. The identification of individual patients at risk of SUDEP is challenging, because interictal cardiac indices are characteristically normal and routine 24-h Holter monitoring is insufficient because it rarely captures an ECG during a seizure. Rugg-Gunn *et al.*[127] implanted a Reveal® Plus loop recorder in patients with refractory partial seizures. In 19 patients, ECG recordings during seizures were collected. The investigators found bradycardia or asystole for which a permanent pacemaker was deemed appropriate in four of the 19 patients. Three of these episodes occurred at the time of a clinical seizure and one was not associated with a known clinical event. Although this is only a pilot study, it shows that cardiac arrhythmias are indeed the culprit in some cases of SUDEP and it suggests that in some patients SUDEP might be preventable by the implantation of a cardiac pacemaker.

Myotonic dystrophy

Myotonic dystrophy, the commonest neuromuscular dystrophy in adults, is a progressive multisystem disorder caused by chromosomal disorder.[128] Heart involvement is common and serious in myotonic dystrophy and SCD is common, occurring with a remarkably high incidence (15–30% of patients) compared with the general population.[129,130] Although its causes in myotonic dystrophy are potentially numerous and have been only rarely determined in an individual patient, progressive deterioration of the cardiac conduction system terminating in heart block and asystole is believed to play a major role. Hardin *et al.*[131] investigated the relationship between autonomic nervous system function, using Holter monitoring with HRV analysis, and the clinical and genetic factors in patients with myotonic dystrophy Type 1. The authors found a decline in HRV with increasing age and the precise genetic abnormality. To date, only very limited data are available regarding the use of Holter monitoring with HRV for routine evaluation of patients with myotonic dystrophy.

Conclusion

Electrocardiographic ambulatory monitoring is an essential tool in the diagnostic evaluation of patients with cardiac arrhythmias. Recent advances in solid-state technology have improved the quality of the ECG signals and new dedicated algorithms have expanded the clinical application of software-based AECG analysis systems. These possibilities have expanded traditional uses of AECG to include arrhythmia monitoring to assess drug and device efficacy, which has been further defined by new studies. However, the analysis of transient ST-segment deviation and measures of HRV remain controversial, but considerably more data are now available, especially about the prognostic value of detecting asymptomatic ischaemia and assessing prognosis. New methods such as analysis of HRT, as a prognostic marker, are promising, but need to be proved in large, prospective clinical trials.

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