Holter monitoring in the prognosis of sudden cardiac death

Okan Erdoğan

Department of Cardiology, School of Medicine, Trakya University, Edirne, Turkey

ABSTRACT

The frequency and rate of either premature ventricular complexes or nonsustained ventricular tachycardia episodes as well as any transient conduction disturbance in a given patient with high risk features for sudden cardiac death (SCD) can be established with Holter monitoring and risk for future cardiac arrhythmic events predicted with reasonable probability. With the aid of published medical literature the present article discussed the role of nonsustained ventricular tachycardia and frequent premature ventricular complexes recorded with long-term Holter electrocardiography in predicting SCD associated with common cardiac disorders such as coronary heart disease, dilated and hypertrophic cardiomyopathy. *(Anadolu Kardiyol Derg 2007: 7 Suppl 1; 64-7)*

Key words: nonsustained ventricular tachycardia, Holter electrocardiography, coronary heart disease, dilated cardiomyopathy, hypertrophic cardiomyopathy, sudden death, arrhythmia

Introduction

Ambulatory Holter electrocardiography (ECG) is a widely used, noninvasive test to evaluate cardiac rhythm problems in various cardiac disorders. Permitting patient ambulatory activity, cardiac rhythm can be continuously examined by Holter ECG throughout the daily activities. One can determine transient and brief episodes of arrhythmias with the aid of two or three leads over a certain time period which is generally either 24 or 48 hours. Recent developments in ambulatory ECG recording provided additional features enabling evaluation of various diagnostic parameters such as ST segment changes, heart rate variability, heart rate turbulence, QT dynamicity and signal averaged ECG (1). These features may help physicians in further establishing risk assessment for sudden cardiac death (SCD). Therefore, Holter ECG is not only a cost-effective tool for arrhythmia assessment, but also very useful in prognostic risk stratification of patients with certain cardiac disorders. The frequency and rate of either premature ventricular complexes (PVC) or nonsustained ventricular tachycardia (NSVT) episodes as well as any transient conduction disturbance in a given patient with high risk features for SCD may well be established with the aid of Holter ECG and risk for future cardiac arrhythmic events can be predicted with reasonable probability. Current concepts of SCD involve electrical, ischemic, mechanical and genetic mutation mechanisms. Central to this viewpoint is activation of the autonomic nervous system by external triggers that lead to an increase in sympathetic tone and a decrease in parasympathetic influences resulting in ischemic or electrical SCD by causing changes in hemodynamics and blood rheology (1). Taken together, SCD may result from either an ischemic event or electrical instability such as ventricular tachycardia or brady-asystole in the presence of autonomic imbalance and factors such as external triggers, abnormal substrate, modulating factors and genomic variability. It is defined as death due to cardiovascular causes in a patient with or without known preexisting heart disease, in whom the mode and time of death are unexpected. The generally accepted temporal definition is up to one hour between the onset of an abrupt change in clinical status and loss of consciousness (1). Although conventional epidemiologic risk markers provide valuable statements about population risk, especially for the development of coronary heart disease, individual risk prediction still remains the major limitation for applying clinically preventive strategies. High risk patient populations studied in the clinical trials of implantable defibrillators constitutes only a small part of the total universe of SCD, and the reported benefits apply only to those small subgroups. Thus, it is very important to find specific risk markers for general population with coronary heart disease, so that a substantial number of patients may derive benefit from interventional therapeutic options (2). In view of the above mentioned basic knowledge and suggestions the present article aims to discuss the role of long-term Holter ECG recording in predicting SCD and risk stratification of patients with various cardiac disorders. Since the prognostic role of other Holter based risk variables such as heart rate variability, heart rate turbulence, signal averaged ECG etc. in risk prediction of SCD is discussed in further sections of this supplement, only trials and investigations regarding complex ventricular arrhythmias such as PVCs and NSVT that might have prognostic significance in specific cardiac disorders by predicting SCD are evaluated and considered in subsequent paragraphs of the present article.

Coronary heart disease, Holter ECG and SCD

Studies suggest that a substantial number (>30%) of all SCDs due to coronary heart disease occur as the first clinical event, and about 33% or more are associated with clinical markers that

Address for Correspondence: Okan Erdoğan, MD, Trakya Üniversitesi Tıp Fakültesi Kardiyoloji Anabilim Dalı, 22030 Edirne, Turkey
Phone: 90 284 235 76 41/4314 Fax: 90 284 235 27 30 E-mail: okanerdogan@yahoo.com

suggest a low risk of event. Only a small proportion of the deaths in this category are defined by high risk markers such as low ejection fraction and ventricular arrhythmias. Hence, strategies that will identify with a much higher level of accuracy within more general subgroups than current indices of individual risk prediction should be developed in order to protect much more patients at risk for SCD with therapeutic interventions (2, 3).

A clinical study conducted in 325 consecutive infarct survivors aimed to investigate the role of NSVT and other variables detected with 24-h Holter monitoring 10 days after myocardial infarction. All patients underwent coronary angiography, determination of left ventricular function and assessment of heart rate variability. Mean follow-up was 30 months. There was a low prevalence (9%) of NSVT shortly after acute myocardial infarction. Nonsustained ventricular tachycardia together with depressed left ventricular ejection fraction (LVEF) was found in only 2.4% of patients. During follow-up, 25 patients reached one of the prospectively defined end points (primary composite end point of cardiac death, sustained ventricular tachycardia or resuscitated ventricular fibrillation; secondary end point: arrhythmic events). The presence of NSVT carried a relative risk of 2.6 for the primary study end point, but was not a significant predictor if only arrhythmic events were considered. On multivariate analysis, only heart rate variability, LVEF and the status of the infarct artery were found to be independently related to the primary study end point. The predictive value of NSVT for subsequent mortality and arrhythmic events is inferior to that of impaired autonomic tone, LVEF or infarct-related artery patency. Accordingly, the use of NSVT to select patients for primary implantable cardioverter /defibrillator prevention trials shortly after acute myocardial infarction appears to be limited (4). A subsequent study involving 700 consecutive patients with acute myocardial infarction was conducted as a prospective observational trial. The end points were total mortality, SCD and non-SCD. Heart rate variability, NSVT, LVEF, baroreflex sensitivity, signal averaged electrocardiogram, QT dispersion, and QRS duration were analyzed. Beta-blocking therapy was used by 97% of the patients at discharge and by 95% at one and two years after myocardial infarction. During a mean follow-up of 43 months, 37 non-SCDs (5.5%) and 22 SCDs (3.2%) occurred. All arrhythmia risk variables differed between the survivors and those with non-SCD. Sudden cardiac death was weakly predicted only by reduced LVEF and NSVT, but not by autonomic markers or standard ECG variables. The positive predictive accuracy of LVEF, NSVT, and abnormal signal averaged electrocardiogram as predictors of SCD was relatively low (8%, 12%, and 13%, respectively). The common arrhythmia risk variables, particularly the autonomic and standard ECG markers, have limited predictive power in identifying patients at risk of SCD after myocardial infarction in the beta-blocking era (5).

A recently published observational clinical study included 2130 patients (mean age 59±10 years) with acute myocardial infarction. The patients were treated with modern therapeutic strategies, for example, 94% were on beta-blocking therapy and 70% underwent coronary revascularization. Various risk parameters from Holter monitoring were analysed. During a median follow-up of 1012 days, cardiac mortality was 113/2130, including 52 SCDs. All Holter variables predicted the occurrence of SCD ($p<0.01$), but only reduced post-ectopic turbulence slope ($p<0.001$) and NSVT ($p<0.01$) remained as marked SCD predictors after adjustment for age, diabetes, and LVEF. In a subgroup analysis, none of the Holter variables predicted SCD among those with LVEF<0.35, but many variables predicted SCD among those with LVEF>0.35, particularly turbulence slope (hazard ratio 5.9; 95% CI 2.9-11.7, $p<0.001$) and NSVT (hazard ratio 3.5; 95% CI 1.5-8.2, $p<0.01$). Therefore, future efforts should also be directed towards interventions aimed at reducing premature SCD among patients with slightly reduced or preserved LV function and abnormal autonomic regulation of heart rate (6).

Another study evaluated the predictive power of heart rate assessed from the standard 12-lead ECG or from Holter recordings for future mortality and arrhythmic events in survivors of acute myocardial infarction. Data from 432 consecutive survivors of acute myocardial infarction were analysed. Heart rate was assessed from a standard 12-lead ECG and from 24-hour Holter recordings obtained at hospital discharge. In addition, LVEF was noninvasively determined. The study end point was prospectively defined as a composite end point comprising mortality and arrhythmic events (ie, sudden death, resuscitated ventricular fibrillation, sustained ventricular tachycardia). Patients were followed for an average of 41 months. Patient age, LVEF, and heart rate were univariate risk predictors of event-free survival. Multivariate analysis by means of a stepwise regression analysis revealed LVEF (11.4, $p=0.0007$), age (9.2, $p=0.02$), and heart rate assessed from the standard 12-lead ECG (7.1, $p=0.008$) as independent risk parameters. Hence, this study revealed that increased heart rate at the time of hospital discharge yields predictive power for subsequent mortality and arrhythmic events. Importantly, heart rate assessed from a conventional ECG carries similar predictive power compared with that determined from the 24-hour mean heart rate obtained from Holter recordings. This predictive power is present despite the high prevalence of beta-blocker therapy in patient population. Whereas at heart rates less than 70 bpm only 3% to 10% of the patients had an event, the proportion of patients with an end point increased to more than 40% in the group of patients with a heart rate of 100 bpm or higher. Simultaneous analysis of patient age, LVEF and heart rate identified a subgroup of acute myocardial infarction survivors at particularly high risk. Accordingly, simple bedside risk stratification at the time of hospital discharge is feasible (7).

As mentioned above, although one large observational study identified NSVT and complex arrhythmias as predictors of SCD in patients with myocardial infarction, it is still controversial whether NSVT might be regarded as an independent predictor for SCD in coronary heart disease.

Dilated cardiomyopathy, Holter ECG and SCD

Ejection fraction is less useful for specifically predicting SCD among patients with dilated cardiomyopathy. In contrast, functional capacity has a better association with SCD. Interestingly, among patients with dilated cardiomyopathy and functional class 1 the risk of dying is small, but the proportional probability that a death will be sudden, if it occurs, is relatively high. There is a large number of such patients at relatively low risk which further limits the predictive power for benefit from interventions (2). Prospective Marburg Cardiomyopathy Study comprised 343 patients with dilated cardiomyopathy and examined the prognostic significance of NSVT episodes on 24- hour Holter ECG (8). During 52 months of follow-up, major arrhythmic events defined as sustained ventricular tachycardia, fibrillation or SCD occurred in 46 of 343

patients (13%). Patients with 3-4 beat runs of NSVT had a similar arrhythmia survival as patients without NSVT on baseline Holter ECG. The incidence of major arrhythmic events during follow-up increased significantly from 2% per year in patients without NSVT to 10% per year in patients with more than 10 beat runs of NSVT ($p<0.05$). Thus, with the aid of this single study one may conclude that the length, but not the rate of NSVT on Holter ECG was a predictor of major cardiac arrhythmic events in patients with dilated cardiomyopathy.

Hypertrophic cardiomyopathy, Holter ECG and SCD

Ventricular tachyarrhythmias, namely NSVT on Holter ECG have been reported as markers for sudden death in highly selected hypertrophic cardiomyopathy populations. However, in non-selected general population with hypertrophic cardiomyopathy the importance of ventricular tachyarrhythmia as a risk marker for SCD is not well established. A clinical study investigated risk markers in 368 patients (14 to 65 years old, 239 males) with hypertrophic cardiomyopathy. There were five variables: NSVT, syncope, exercise blood pressure response (BPR), family history of sudden death (FHSD) and left ventricular wall thickness (LVWT). During follow-up of mean 3.6 years (range 2 days to 9.6 years), 36 patients (9.8%) died, 22 of them suddenly. Two patients received heart transplants. The six-year sudden death free survival rate was 91% (95% confidence interval [CI] 87% to 95%). In the Cox model, there was a significant pair-wise interaction between FHSD and syncope ($p=0.01$), and these were subsequently considered together. The multivariate sudden death risk ratios (with 95% CIs) were 1.8 for BPR (0.7 to 4.4) ($p=0.22$); 5.3 for FHSD and syncope (1.9 to 14.9) ($p=0.002$); 1.9 for NSVT (0.7 to 5.0) ($p=0.18$) and 2.9 for LVWT (1.1 to 7.1) ($p=0.03$). Patients with no risk factors (n=203) had an estimated six-year sudden death free survival rate of 95% (95% CI, 91% to 99%). The corresponding six-year estimates (with 95% CIs) for one (n=122), two (n=36) and three (n=7) risk factors were 93% (87% to 99%), 82% (67% to 96%) and 36% (0% to 75%), respectively. Patients with two or more risk factors had a lower six-year sudden death survival rate (95% CI) compared with patients with one or no risk factors (72% [56% to 88%] vs. 94% [91% to 98%]) ($p=0.0001$). This study demonstrates that patients with multiple risk factors have a substantially increased risk of sudden death sufficient to warrant consideration for prophylactic therapy (9).

It has been suggested that NSVT is only of prognostic importance in patients with hypertrophic cardiomyopathy when repetitive, prolonged, or associated with symptoms. In one study, 531 patients with hypertrophic cardiomyopathy underwent Holter ECG monitoring mean duration of 41 hours. A total of 104 patients (19.6%) had NSVT. The proportion of patients with NSVT increased with age ($p=0.008$). Maximum left ventricular wall thickness and left atrial size were greater in patients with NSVT. Mean follow-up was 70 months. Sixty-eight patients died, 32 from SCD. Twenty-one patients received an implantable cardioverter defibrillator. There were four appropriate defibrillator discharges. In patients less than 30 years, five-year freedom from sudden death was lower in those with NSVT (77.6% [95% CI: 59.8 to 95.4] vs. 94.1% [95% CI: 90.2 to 98.0]; $p=0.003$). There was no relation between the duration, frequency, or rate of NSVT runs and prognosis at any age. The odds ratio of sudden death in patients less than 30 years of age with NSVT was 4.35 (95% CI: 1.54 to 12.28; $p=0.006$) compared with 2.16 (95% CI: 0.82 to 5.69; $p=0.1$) in patients more than 30 years of age. Nonsustained ventricular tachycardia is associated with a substantial increase in sudden death risk in young patients with hypertrophic cardiomyopathy. A relation between the frequency, duration, and rate of NSVT episodes could not be demonstrated (10).

A clinical study was undertaken in order to assemble a profile and assess the significance of arrhythmias in a nontertiary-based hypertrophic cardiomyopathy cohort. The profile of ventricular/supraventricular ectopy and bradyarrhythmia were assessed on 24-h Holter ECG and also related these findings to clinical outcome in 178 patients. Of the 178 study patients, including 21 (12%) with>500 PVCs, 74 (42%) had couplets, 67 (37%) had supraventricular tachycardia, and 56 (31%) had NSVT. Mean number of PVCs was 330±763 (range 1 to 5.435) and increased with age ($p<0.01$). Nonsustained ventricular tachycardia was associated with greater left ventricular hypertrophy ($p=0.01$) and severe symptoms (functional classes III and IV) ($p=0.04$); supraventricular tachycardia occurred more commonly in patients with outflow obstruction ($p=0.02$). Over a follow-up of 5.5±3.4 years, 11 (6%) patients died suddenly (annual mortality rate, 1.1%) including 5 patients with NSVT. For sudden death, NSVT on Holter ECG had negative and positive predictive values of 95% and 9%, and sensitivity and specificity of 45% and 69%, respectively. In this nontertiary-based cohort group, ventricular and supraventricular tachyarrhythmias were particularly frequent and demonstrated a broad spectrum on Holter ECG. Paradoxically, despite such a highly arrhythmogenic substrate, sudden death events proved to be relatively uncommon. Ventricular tachyarrhythmias had a low positive and relatively high negative predictive value for sudden death in this population (11).

Other cardiac disorders

A recent study investigated the prognosis and SCD risk in a cohort of 100 patients with bifascicular block. During a median follow-up of 84 months, 33 patients died. Fourteen patients died of SCD. In a univariate analysis, advanced age, a previous myocardial infarction, and heart failure were associated with a significantly increased risk of all-cause mortality and SCD. In a Cox multiple regression analysis, heart failure was the only independent predictor of all-cause mortality and SCD ($p<0.01$). Holter ECG did not reveal any tachy- or brady-arrhythmic episodes indicating its poor role in identifying high risk bifascicular block patients regarding long-term prognosis. No significant association between pacemaker treatment and the incidence of death was observed. Patients with bifascicular block have a poor long-term prognosis. The predictive value of noninvasive and invasive investigations is limited. The only independent predictor of all-cause mortality and SCD in this population was the presence of heart failure (12).

Holter ECG was used in another interesting clinical study conducted in trained athletes. Given the high incidence of SCD among trained athletes mediated by ventricular tachyarrhythmias, the impact of athletic training and physical deconditioning on frequent and/or complex ventricular tachyarrhythmias were assessed by 24-hour Holter ECG. Holter ECGs were recorded at peak training and after a deconditioning period of 19±6 weeks (range, 12 to 24 weeks) in a population of 70 trained athletes selected on the basis of frequent and/or complex ventricular tachyarrhythmias. A significant decrease in the frequency and complexity of ventricular arrhythmias was evident after deconditioning. In 50 of the 70 athletes (71%), ventricular arrhythmias

decreased substantially after detraining. Most of these athletes with reduced arrhythmias did not have structural cardiovascular abnormalities (37 of 50; 74%). Over the 8±4-year follow-up period, each of the 70 athletes survived without cardiac symptoms. The authors concluded that frequent and/or complex ventricular tachyarrhythmias in trained athletes (with and without cardiovascular abnormalities) are sensitive to brief periods of deconditioning. In athletes with heart disease, the resolution of such arrhythmias with detraining may represent a mechanism by which the risk for sudden death is reduced. Conversely, in athletes without cardiovascular abnormalities, reduction in frequency of ventricular tachyarrhythmias and the absence of cardiac events in the follow-up support the benign clinical nature of these rhythm disturbances as another expression of athlete's heart (13).

In conclusion, long-term Holter ECG recording has an important role in predicting SCD by providing useful information about the frequency, rate and type of NSVT as well as complex PVCs. However, the risk of SCD should be carefully interpreted according to specific cardiac disorder and additional risk factors.

References

1. Kennedy HL. Use of long-term (Holter) electrocardiographic recordings. In Zipes DP, Jalife J, editors. Cardiac Electrophysiology: From Cell to Bedside, 4th edition. Philadelphia; WB Saunders: 2004. p. 772-87.
2. Myerburg RJ, Interian A, Simmons J, Castellanos A. Sudden cardiac death. In Zipes DP, Jalife J, editors. Cardiac Electrophysiology: From Cell to Bedside, 4th edition. Philadelphia; WB Saunders: 2004. p. 720-31.
3. Myerburg RJ. Sudden cardiac death: Exploring the limits of our knowledge. J Cardiovasc Electrophysiol 2001; 12: 369-81.
4. Hohnloser SH, Klingenheben T, Zabel M, Schopperl M, Mauss O. Prevalence, characteristics and prognostic value during long-term follow-up of nonsustained ventricular tachycardia after myocardial infarction in the thrombolytic era. J Am Coll Cardiol 1999; 33: 1895-902.
5. Huikuri HV, Tapanainen JM, Lindgren K, Raatikainen P, Makikallio TH, Airaksinen KJ, et al. Prediction of sudden cardiac death after myocardial infarction in the beta-blocking era. J Am Coll Cardiol 2003; 42: 652-8.
6. Makikallio TH, Barthel P, Schneider R, Bauer A, Tapanainen JM, Tulppo MP, et al. Prediction of sudden cardiac death after acute myocardial infarction: role of Holter monitoring in the modern treatment era. Eur Heart J 2005; 26: 762-9.
7. Mauss O, Klingenheben T, Ptaszynski P, Hohnloser S. Bedside risk stratification after acute myocardial infarction: Prospective evaluation of the use of heart rate and left ventricular function. J Electrocardiol 2005; 38: 106-12.
8. Grimm W, Christ M, Maisch B. Long runs of non-sustained ventricular tachycardia on 24-hour ambulatory electrocardiogram predict major arrhythmic events in patients with idiopathic dilated cardiomyopathy. Pacing Clin Electrophysiol 2005; 28 (Suppl): S207-10.
9. Elliott PM, Poloniecki J, Dickie S, Sharma S, Monserrat L, Varnava A, et al. Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. J Am Coll Cardiol 2000; 36: 2212-8.
10. Monserrat L, Elliott PM, Gimeno JR, Sharma S, Penas-Lado M, McKenna WJ. Non-sustained ventricular tachycardia in hypertrophic cardiomyopathy: an independent marker of sudden death risk in young patients. J Am Coll Cardiol 2003; 42: 873-9.
11. Adabag AS, Casey SA, Kuskowski MA, Zenovich AG, Maron BJ. Spectrum and prognostic significance of arrhythmias on ambulatory Holter electrocardiogram in hypertrophic cardiomyopathy. J Am Coll Cardiol 2005; 45: 697-704.
12. Tabrizi F, Rosenqvist M, Bergfelt T, Englund A. Long-term prognosis in patients with bifascicular block - the predictive value of noninvasive and invasive assessment. J Intern Med 2006; 260: 31-8.
13. Biffi A, Maron BJ, Verdile L, Fernando F, Spataro A, Marcello G, et al. Impact of physical deconditioning on ventricular tachyarrhythmias in trained athletes. J Am Coll Cardiol 2004; 44: 1053-8.