The Usefulness of Holter Monitoring in the Evaluation of Antiarrhythmic Drug Efficacy for Tachycardia

TAKASHI YANAGA, M.D., YUHEI ICHIMARU, M.D., TERUNORI UENO, M.D.
YOICHI HATA, M.D., KENJI OKAMOTO, M.D., YASUYUKI KODAMA, M.D.
and KUNIHIKO OTSUKA, M.D.*

Using Holter monitoring tachycardia was found in 145 out of 2058 patients suffering from various underlying diseases. Three thousand seven hundred and forty monitorings were performed. The mean age of patients was 54.5 years with a range of 19 to 83 years. The observed tachycardia was classified into three types: tachycardia with short duration, tachycardia with long duration and tachycardia with complex form. The attacks of tachycardia were more frequently observed during periods of physical activity than during sleeping periods. The relationship of the number of tachycardia with short duration between 24-hour Holter monitorings was examined in order to establish day to day variability of the attacks. The 95% confidence interval about the resultant regression line was calculated and the percent reduction required for the evaluation of drug efficacy to avoid the chances of interference of spontaneous variation was found to be about 44.0, 55.0 and 82% when the total number of attacks during a 24-hour period were 50, 100 and 1,000, respectively. Holter monitoring showed higher positive results as compared to exercise testing for detection of tachycardia. Higher correlation coefficients between numbers of premature ventricular contractions (PVCs) and the plasma concentrations of procainamide or N-acetylprocainamide were observed in 3 or more successive PVCs than in individually occurring PVCs. Using repeated 24-hour Holter monitorings a significant reduction in the number of tachycardia was observed when the therapeutic concentration was reached after the combined or single administration of the drug.

These results suggest that repeated Holter monitorings, exercise testing and determination of plasma level of the drug may be useful for the evaluation of antiarrhythmic drug efficacy for tachycardia.

Effective management of tachycardia is an important problem in the treatment of cardiac patients. There are two acceptable techniques for clinical evaluation of antiarrhythmic drugs. One of these is an electrophysiological method for induction of arrhythmias and the other is Holter monitoring. The former offers a method for quantitative measurement of refractory period, theshold and conduction velocity. The latter permits the accurate recordings of all attacks during daily life. Using Holter monitoring Morganroth and his coworkers1 have reported

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Department of Bioclimatology and Medicine, Medical Institute of Bioregulation, Kyushu University, Beppu;
*Department of Physiology, Kochi Medical School, Nankoku, Japan
Mailing address: Takashi Yanaga, M.D., Department of Bioclimatology and Medicine, Medical Institute of Bioregulation, Kyushu University, Beppu 874, Japan

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the limitations of routine long-term electrocardiographic monitoring to assess ventricular ectopic frequency. Michelson and his coworkers have shown spontaneous variability of complex ventricular arrhythmias. Sami and his coworkers have reported a new method for evaluating antiarrhythmic efficacy. There are few reports on the evaluation of the efficacy of antiarrhythmic drugs for tachycardia using Holter monitoring. The present study was performed to clarify the actual status of the tachycardia attacks and to examine the usefulness of Holter monitoring in the evaluation of antiarrhythmic drug efficacy.

METHODS

The 24-hour, long-term ambulatory electrocardiographic recordings were obtained from 2,058 patients using a one-channel or two-channel recorder (Avionics, Model 400 or 445). The total number of monitorings was 3,740. The patients' ages ranged from 19 to 83 years (mean ± standard deviation, 54.5 ± 14.5 years). Diagnoses included ischemic heart disease in 71 patients, congestive cardiomyopathy in 11, valvular heart disease in 4, congenital heart disease in 5, no structural change in 5 and others in 15. In others, hypertension and pulmonary

A. Short Duration
E.T. 52 yrs. Female

B. Long Duration
T.K. 51 yrs. Male

C. Complex Form
S.T. 52 yrs. Male

Fig.1. Three types of tachycardia.
Tachycardia was differentiated by their duration into 2 types: short duration which persists less than one hour and long duration which persists more than one hour. When tachycardia shows various types of arrhythmias such as supraventricular or ventricular tachycardia and when their differentiation is very difficult and countless, it is referred to as complex form.
disease were included (Table I). Avionics tape was analyzed using an Avionics 660A Electrocadioscanner with minicomputer. Electrocardiovalidator and Model 9200 VIS-U-SCAN (Del Mar Avionics) were also used to print out all electrocardiograms for a 24-hour period and the attacks of tachycardia were verified by a cardiologist directly. In 527 patients, exercise testing was done by using a treadmill or bicycle ergometer. In some cases the plasma levels of antiarrhythmic drugs were also measured. For statistical analysis the Student’s t-test was used and the confidence interval was calculated using the method reported by Johnson and his coworkers.

RESULTS

Nature of Tachycardia

On Holter monitoring three types of tachycardia could be differentiated: tachycardia with short duration, tachycardia with long duration and tachycardia with complex form as shown in Fig. 1. The tachycardia of less than one hour in duration was defined as tachycardia with short duration, and longer than one hour, as tachycardia with long duration. The tachycardia with countless arrhythmias was defined as tachycardia with complex form. Figure 2 shows the relationship between these types of tachycardia and the prognosis. Complications such as death, myocardial infarction and cerebral thromboembolism were found in all types of tachycardia except paroxysmal supraventricular tachycardia with short duration. Figure 3 shows the circadian variation of the time of the beginning of the attacks. Five hundred and ninety-seven attacks of tachycardia with short duration in 17 patients and 776 attacks of tachycardia with long duration in 21 patients were analyzed. Preferential occurrence of attacks during physical activities is clearly observed. Figure 4 shows the correlation between numbers of premature ventricular contractions (PVCs) observed in each hour in 24 hours and the total PVC numbers observed in 24 hours in 15 patients. Significant correlations for
3 or more successive PVCs were demonstrated during the period from 5:00 a.m. to 8:00 p.m. Figure 5 shows the comparison of diagnostic efficiency of tachycardia between Holter monitoring and exercise testing. Both tests were done in 527 cases and tachycardia was observed in 19 cases. Holter monitoring showed higher positive results as compared to the exercise test. However, in 4 cases Holter monitoring showed negative results, while the exercise test showed positive results. This indicates that both methods are complementary for the effective detection of arrhythmias. Figure 6 shows the relationship between sleep stages and occurrence of tachycardia in 9 patients. Sleep stages were determined by the international classification of Rechtschaffen. Tachycardia attacks were frequently observed during awake periods and rapid eye movement (REM) sleep, indicating more frequent occurrence during physical and psychic activities. Figure 7 shows the relationship of numbers of tachycardia with short duration between the first day and the second day of Holter monitorings. No antiarrhythmic drugs were given to these patients before the monitorings. The linear regression analysis was done and a 95% confidence interval was calculated to establish natural variation of attacks of tachycardia. The regression line, \( Y = 0.44 + 0.71X \), was obtained, where \( Y = \log(n+1) \) on the second day, \( X = \log(n+1) \) on the first day, and \( n \) = numbers of tachycardias observed. The 95% confidence interval about the regression line was between \( 0.44 + 0.71X + 1.21 \times \sqrt{1/49 + (X - 1.28)^2/51} \) and \( 0.44 + 0.71X - 1.21 \times \sqrt{1/49 + (X - 1.28)^2/51} \). Thus, the percent
reduction required for the evaluation of the drug efficacy to avoid the chances of interference by spontaneous reduction was 44.0, 55.0 and 82.0% when the numbers of tachycardia were 50, 100 and 1,000, respectively, for a 24-hour period.

**Evaluation of the Efficacy of Antiarrhythmic Drugs**

Table II shows the relationship between plasma concentration of procainamide or N-acetylprocainamide and PVC frequencies in a patient with congestive cardiomyopathy. One monitoring was done before administration of the drug, and successive monitorings were done after the administration of the drug in doses of 1, 2 and 2.5 g. Four or six determinations of plasma level of the drug were made during 24-hour Holter monitoring. The numbers of each type of PVC during various one hour intervals were plotted against the plasma concentration during that interval and the correlation coefficient was calculated. A higher correlation coefficient was obtained with respect to the 3 or more successive PVCs as compared to nonsuccessive PVCs. This may show that procainamide and N-acetylprocainamide show similar action but the drugs do not necessarily show additive action and 3 or more successive PVCs show higher sensitivity to drugs as compared to nonsuccessive PVCs. On the other hand, two successive PVCs increased in number after the drug administration. Figure 8 shows a double blind test for mexiletine in a case with ventricular tachycardia. As shown in Fig. 8B monitorings were done before the drug administration, indicating that occurrence of tachycardia has reproducibility. In Fig. 8C a placebo was given and tachycardia was also observed. On the other hand, no tachycardia was observed after the administration of mexiletine or disopyramide in 5 monitorings (Fig. 8D). As shown in Fig. 8E, reappearance of attacks was observed after the test. Figure 9 shows the results of exercise testing before and after the drug administration in the same case as in Fig. 8. After the administration of the drug, attacks were not induced by the exercise test. Increases in heart rate, systolic blood pressure, pressure rate product and oxygen consumption (VO2) for
the same workload were observed after the administration of the drug. Figure 10 shows the effect of mexiletine or disopyramide on chronic, recurrent tachycardia attacks after 2 weeks of the administration of the drug. In this case, 2 monitorings were done one before and one after the drug administration. As shown in Fig. 10B a reduction of more than 80% was observed in the number of attacks after the drug administration. Both drugs produced a significant increase in the preceding R-R interval. Disopyramide induced significant increases in coupling time and sinus node recovery time, while mexiletine did not. The determination of peak plasma concentration showed that it was within therapeutic range after the administration of the drug.

Figure 11 shows the combined treatment with diltiazem and procaainamide in WPW syndrome with chronic, recurrent tachycardia. Procaainamide in the doses from 2.0 to 2.25 g increased the number and the duration of the attacks. Thus, diltiazem was given additionally to procaainamide and a decrease in the number of attacks was observed. Then, the procaainamide dose was further increased to 2.5 g, and the number of attacks was significantly decreased. The mean duration of tachycardias was also decreased, but it was not statistically significant. The plasma concentration of procaainamide and N-acetylprocaainamide after the 2.0 g administration of the drug was similar in value to that after the 2.5 g administration of the drug.

Figure 12 shows the treatment with diphenylhydantoin, propranolol alone and the combined treatment with these drugs in a patient with long QT syndrome. Propranolol alone did not abolish ventricular tachycardia or fibrillation. Diphenylhydantoin blocked the occurrence of attacks, however, palpitation remained. After the administration of both drugs, attacks as well as subjective symptoms were completely abolished.

Digitalis is frequently administered to treat

supraventricular tachycardia. Thus, the effects of oral administration of digoxin (0.25 mg/day) on frequency, duration and corrected automaticity recovery time (CART) in recurrent supraventricular tachycardia were studied in 7 patients (Fig. 13). Two or three monitorings were performed before and after the drug administration in each case. In 5 of 6 patients, frequency of the attacks was decreased, in 6 of 7 patients the duration was decreased and in 4 of 6 patients, CART was increased.

DISCUSSION

To establish the efficacy of antiarrhythmic drugs used for tachycardia, the characteristics such as definition, prognosis and natural variation must be clarified. In this study, tachycardia could be classified into three types: tachycardia with short duration (lasting less than one hour), tachycardia with long duration (lasting greater than one hour) and tachycardia with complex form. Generally, for the quantitative description of arrhythmias, the number of tachycardia during each hour for a 24-hour period is a very useful parameter. According to our definition, in tachycardia with short duration the description of preferential occurrence of attacks is possible. Furthermore, in tachycardia with short or long duration, the drug efficacy can be evaluated by measuring the decrease in number of tachycardia. On the other hand, such an analysis cannot be done in tachycardia with complex form. Complications such as death, myocardial infarction and thromboembolism were observed in all types of tachycardia except paroxysmal supraventricular tachycardia with short duration. In a case of tachycardia with complex form, cerebral embolism occurred during the course of the disease. In this case, permanent pacemaker implantation was done and the tachycardia was almost completely eliminated. This may indicate that our definition of tachycardia has a prognostic significance, although the clinical significance must be further studied.

| TABLE II | RELATIONSHIP BETWEEN PVC NUMBERS FOR EACH GRADE AND THE CONCENTRATIONS OF PROCAINAMIDE, N-ACETYLPRAOCAINAMIDE, OR THE COMBINATION OF THE DRUGS |
|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Plasma conc. | PVC grade | \( r \) | \( p \) value |
| PA | vs | PVC (1) | -0.3598 | < 0.01 |
| PA | vs | PVC (2) | 0.2314 | < 0.05 |
| PA | vs | PVC (3 <) | -0.5430 | < 0.01 |
| NAPA | vs | PVC (1) | -0.4228 | < 0.01 |
| NAPA | vs | PVC (2) | 0.2463 | < 0.01 |
| NAPA | vs | PVC (3 <) | -0.6179 | < 0.01 |
| PA + NAPA | vs | PVC (1) | -0.3821 | < 0.01 |
| PA + NAPA | vs | PVC (2) | 0.2444 | < 0.01 |
| PA + NAPA | vs | PVC (3 <) | -0.5869 | < 0.01 |

\( n = 34 \) (\( n \): number of determination of plasma level of the drugs). \( PA = \) procainamide, \( NAPA = \) N-acetylpcaoinamide, \( Plasma \ conc. = \) plasma concentration of the drugs.
T.E. 51 yrs. Female VT No organic heart disease

Fig. 8. Double blind test on the efficacy of mexiletine.
Upper tracing: electrocardiogram during tachycardia attack. Lower tracing B: number of VT (ventricular tachycardia) before test; C: number of VT during placebo administration; D: number of VT during mexiletine or disopyramide administration; E: after test (no drug administration). n = number of monitorings.

The natural variation of arrhythmias must be clarified for the evaluation of the antiarrhythmic drug efficacy. Important factors which affect the natural variation are exercise and sleep. In this study the tachycardia was more frequently observed during waking periods than during sleeping periods. Concerning the relationship between sleep and premature beat, Lown and his coworkers have found that in most patients sleep was associated with a lowered occurrence of ventricular premature contraction. In our study there was no definite correlation between the appearance of tachycardia and sleep stage. In 2 patients the number of tachycardia was markedly increased in the REM stage. A higher correlation coefficient was obtained between the number of tachycardia observed during each hour from 5:00 a.m. to 8:00 p.m. and the total number observed during a 24-hour period, than between the number observed in the nighttime and the total number during a 24-hour period. Above-mentioned results suggest that the initiation of attacks has an intimate relationship between physical and psychic activities. This also means that although tachycardia has great natural variation, recording in the daytime is useful for the evaluation of the total number of tachycardia for a 24-hour period. In this study Holter monitoring and exercise testing were compared for diagnostic efficiency of the tachycardia. Holter monitoring showed higher positive results as compared to the exercise test. However, in 4 cases, Holter monitoring was negative, while the exercise test was positive. Force and his coworkers have reported that the use of both monitoring and exercise testing enhances a detection of arrhythmias in patients with symptomatic preexcitation. Kennedy has stated that

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ambulatory electrocardiography is more sensitive than exercise testing in detecting cardiac arrhythmias. These results suggest that both methods are complementary for the detection of arrhythmias. In this study exercise induced tachycardia before the administration of antiarrhythmic drugs, while after the administration of the drug it did not (Fig. 9). Recently, Sheps and his coworkers have observed a decrease in frequency of exercise-induced ventricular ectopic activity in the second of two consecutive treadmill tests. This indicates that tests of effectiveness of an antiarrhythmic drug should not be based solely on a decrease in the amount or severity of ventricular irritability between two successive exercise tests, one immediately before and the other following administration of the drug. This suggests that for the confirmation of the drug efficacy by the exercise test the reproducibility must be examined. However, it is sometimes difficult to observe the reproducibility, because there may be a risk of an appearance of more severe arrhythmias.

Statistical analysis of arrhythmias has shown that marked spontaneous hour-to-hour or day-to-day variability in arrhythmia frequency may occur in individual patients. Thus, to determine the antiarrhythmic drug efficacy reduction must exceed such a spontaneous variation statistically. Morganroth and his coworkers have reported that to distinguish a reduction in PVC frequency attributable to therapeutic intervention rather than biologic or spontaneous variation alone required a reduction in PVC frequency greater...
than 83% if only two 24-hour monitoring periods were compared, and a reduction greater than 65% if two 72-hour periods were compared. Michelson and his coworkers have shown that comparing a 24-hour test period with a 24-hour control period would require a 65% decrease in mean hourly frequency of ventricular tachycardia and 75% reduction in the frequency of couplets to demonstrate therapeutic efficacy rather than a reduction due to spontaneous reduction alone. Sami and his coworkers have shown that to establish antiarrhythmic drug efficacy with 95% confidence, the minimal percent reduction of PVCs between baseline and placebo trials was 65% for ambulatory electrocardiography. He has also reported that the lower limit of baseline PVC frequency for which the procedure could distinguish a placebo from a true drug response was an average frequency of 2.2 PVCs/hour for ambulatory electrocardiographic monitoring, that is 53 PVCs per 24-hour period. In the present study the percent reduction required to differentiate drug efficacy from spontaneous reduction was 44.0, 55.0 and 82% when the numbers of tachycardia were 50, 100 and 1,000, respectively, for a 24-hour period. As a general rule, patients with less frequent ventricular ectopic activity will require a greater suppression than those who have more frequent ectopic beats, while in this study patients with fewer

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tachycardia required a lower percentage reduction to determine drug efficacy than patients with more frequent tachycardia. These differences from other reports may possibly be explained by considering the differences in nature between PVCs and tachycardia, differences in patient groups and applicability of statistical methods. In our patient series, the frequency of tachycardia was higher in the second day than in the first day in 24 out of 49 patients and it showed no change in 6 out of 49 patients. Our study suggests that for the establishment of the criteria for the drug efficacy for tachycardia it is necessary to construct a data base with large and different patient groups.

The purpose of administration of antiarrhythmic drugs is an abolition of attacks, a decrease in ventricular rate, treatment or prevention of cardiac decompensation, treatment for subjective symptoms, prevention of attacks and sudden death, and prevention of myocardial infarction and cerebral embolism. Stern and his coworkers have reported that sudden death was more frequent in individuals without ischemic heart disease if ambulatory electrocardiographic monitoring disclosed ventricular arrhythmia, as compared to individuals without ventricular arrhythmia. On the other hand, Camm and his coworkers have demonstrated that ectopic cardiac rhythm and arrhythmias are more common in
Fig. 12. Effect of diphenylhydantoin, propranolol or the combination on ventricular tachycardia in a case with long-QT syndrome. A: electrocardiogram at the initiation of an attack of ventricular tachycardia; B: electrocardiogram at the termination of an attack of ventricular tachycardia; C: Effects of diphenylhydantoin, propranolol or the combination on heart rate, QTc and oxygen consumption (VO2). VF = ventricular fibrillation.
higher mortality rate is related to severe cardiac disease rather than to the presence of ventricular runs. Lie and his coworkers\textsuperscript{14} have reported that the presence of warning arrhythmias is not helpful in deciding whether or not antiarrhythmic therapy should be instituted. At the present stage, the indication of antiarrhythmic agent must be determined according to the individual patient, after the deliberate consideration of the advantages and disadvantages of the use of any particular antiarrhythmic drugs.

Recently, Merburg and his coworkers\textsuperscript{15} have reported that the relationship between plasma levels of procainamide and PVC suppression appeared to be different in acute myocardial infarction and chronic ischemic heart disease patients; furthermore, a high degree of PVC suppression is not a necessary endpoint of antiarrhythmic therapy when attempting to protect patients against recurrent symptomatic ventricular tachycardia. Krone and his coworkers\textsuperscript{16} have also reported that in 12 patients no antiarrhythmic agent induced a significant overall reduction in number of PVCs, but both quinidine and procainamide showed a statistically significant reduction of PVCs with coupling intervals of less than 400 msec. These findings demonstrate that clinically important effects of antiarrhythmic drugs can occur in the absence of an overall reduction in the number of PVCs. In this study, the reduction of 3 or more successive PVCs showed a higher correlation coefficient to procainamide or N-acetylpromacainamide than the reduction of nonsuccessive PVCs, although the reduction of 2 successive PVCs did not show any correlation with the plasma concentration of the drugs. Our results may be partially explained by considering the difference in sensitivity to drugs between nonsuccessive and successive PVCs.

In this study, using repeated 24-hour monitorings, it was shown that significant reduction in the number of tachycardia after the drug administration was useful for the evaluation of the antiarrhythmic drugs. Furthermore, the measurement of plasma level of drugs was useful for the determination of the therapeutic effect. The combined treatment with procainamide and diltiazem hydrochloride was useful in WPW syndrome with recurrent and chronic tachycardia. In a case with long QT syndrome with recurrent tachycardia, the combined administration of propranolol and diphenyhydantoin induced a marked improvement, which was apparent by the observation of various parameters such as frequency and duration of tachycardia, subjective symptoms and blood pressure. It was shown that digitalis is effective but in several cases showed an increase in number of tachycardia, indicating the necessity of individualization of drug administration. A pooled study of the effectiveness of antiarrhythmic drugs would be valuable with respect to the efficacy of new drugs, especially those with only a small number of 24-hour monitorings. This would give an improved statistical analysis and could minimize the effect of spontaneous variation on individual
tachycardia patients. Recently, such studies are increasing in number.\textsuperscript{17,18}

The above-mentioned discussion suggests that at least two Holter monitorings are necessary before drug administration for the evaluation of antiarrhythmic drug efficacy for the tachycardia; exercise testing is complementary with 24-hour ECG monitoring for the detection of arrhythmias, and the determination of plasma level of the drug is useful for the evaluation of the change in number of tachycardia.

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