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ORIGINAL ARTICLE

Prognostic value of the sinoatrial conduction time measured by the Holter method. Results of a prospective follow-up study

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Abstract

Background: *To evaluate the usefulness of the Holter method of sinoatrial conduction time (SACT) calculation in predicting the future occurrence of sinus node disease, and the emergence of indications for permanent pacing in patients with unexplained syncope.*

Methods: *The study group included 218 patients (mean age 55 ± 17 years, 116 men) with syncope of unknown etiology in whom spontaneous atrial premature depolarizations (APDs) occurred during Holter monitoring and SACT could be calculated. A SACT value during daily activity > 150 ms was assumed as abnormal.*

Results: *The prospective observation time was 48 ± 11 months. During follow-up sinus node disease was diagnosed in 22 persons, including 18 patients with baseline SACT > 150 ms and 4 with SACT < 150 ms. Indications for pacemaker implantation were found in 16 patients, including 13 patients with baseline SACT > 150 ms and 3 with SACT < 150 ms. In subjects with and without sinus node disease diagnosed during the observation period, baseline SACT values were 175 ± 52 ms and 87 ± 34 ms, respectively (p < 0.01), and in patients qualified and not qualified for permanent pacing, the respective values were 178 ± 59 ms and 81 ± 38 ms (p < 0.01). Multivariate Cox analysis showed a significant relationship between baseline SACT > 150 ms and a future diagnosis of sinus node disease and pacemaker implantation.*

Conclusions: *The results suggest that the Holter method of SACT calculation is useful in predicting sinus node disease and indications for permanent pacing in patients with unexplained syncope.* (Cardiol J 2013; 20, 5: 539–544)

Key words: Holter monitoring, sinoatrial conduction time, prognosis

Introduction

A high rate of unexplained syncope in various clinical settings, involving enormous resources for diagnosis and therapy, justifies the constant search for effective evaluation strategies. In most patients with syncope, electrocardiography (ECG) findings established as diagnostic [1] do not recur during the 24-h ECG monitoring period. Thus, the true yield of the standard Holter ECG assessment in an unselected population is as low as 1–2%.

The sinoatrial conduction time (SACT) is the interval between the activation of the sinus node and the beginning of depolarization of the right atrium muscle or the P-wave beginning in an ECG. This time is not constant and varies throughout the day under the influence of the autonomic system; it extends during the night, and shortens during daytime activity [2]. The range limits are not definitively established. It can be assumed that the normal SACT usually does not exceed 150 ms in an awake patient. SACT measurements are

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usually performed with various modifications of the Strauss' method [3–6]. This indirect approach involves the introduction of progressively premature atrial depolarization during a stable sinus rhythm and measurement of the first return cycle. The measurement is taken for atrial premature depolarizations (APDs) falling into the reset zone, that is, the range of coupling intervals at which reset of the sinus node occurs [7]. The Holter method of SACT estimation is rarely used. Instead of being induced, it applies the spontaneous APDs recorded in ECG Holter monitoring during daytime activity [2]. One of the reasons for the low prevalence of this simple and noninvasive method is the lack of studies determining the prognostic significance of Holter SACT values on the basis of a prospective follow-up.

The aim of the study was to determine the prognostic value of SACT calculated by the Holter method in predicting the future diagnosis of sinus node disease, the occurrence of indications for permanent pacing and the risk of death in patients with unexplained syncope.

Methods

Study population

The initial study population consisted of 300 patients with unexplained syncope who presented sinus rhythm in 24-h Holter ECGs. Unexplained syncope was defined as a transient loss of consciousness characterized by rapid onset, short duration, and spontaneous complete recovery whose cause was not established based on careful history, physical examination, standard ECG, or 24-h ECG Holter monitoring. Patients with atrioventricular block I–III° and those treated with digitalis glycoside or group I or III antiarrhythmic drugs according to the Vaughan-Williams classification were excluded.

Finally, 218 patients (73% of the baseline number) in whom the Holter study showed APDs eligible for SACT calculation met the inclusion criteria. The average age was 55 ± 17 (19–85) years.

All of the patients were thoroughly informed of the study and signed a written informed consent form approved by the Institutional Committee on Human Research.

SACT calculation and follow-up

For measurement purposes, a fragment of the ECG with spontaneous APD that occurred during daytime within a stable sinus rhythm in which the post-extrasystolic interval was less than the compensatory length was selected (Fig. 1). The SACT was calculated as half the difference between the return cycle length after spontaneous APD (P2-P3) and sinus cycle length (P1-P1).

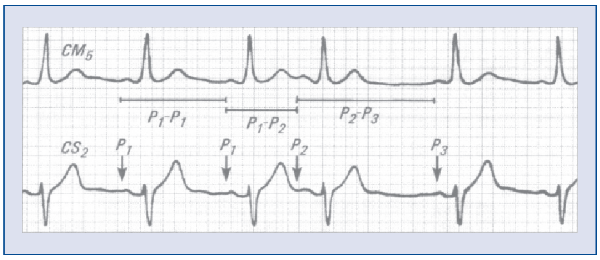

Figure 1. Method of a non-invasive calculation of the sinoatrial conduction time.

Measurements were performed based on the first Holter ECG fragment with APD that fulfilled the following criteria:

1. APD occurred during stable sinus rhythm, that is, the differences in cycle length between 3 consecutive preceding PP intervals were lower than 20 ms.
2. The APD coupling interval was longer than 50% of the preceding sinus cycle length.
3. The sum of the APD coupling interval and the postextrasystolic pause was shorter than the sum of two spontaneous sinus cycle lengths.
4. APD had a positive P wave in lead CM5.

If these criteria were fulfilled, the reliability of SACT calculation was assumed and only one measurement per patient was performed.

Based on prior studies in which the Holter method was applied for SACT measurement, the value of 150 ms was taken as the optimal point of dichotomic distribution for prognostic purposes [2]. During a prospective follow-up, patients were subjected to clinical assessment and 24-h Holter monitoring in 12-month intervals. An observation endpoint was the patient's death. The hospital diagnosis of sinus node disease and the emergence of indications for permanent pacing were also noted. These outcomes were established during follow-up according to the current guidelines and were blinded to SACT values obtained from the baseline 24-h Holter ECG monitoring. For deaths (overall mortality), the date and nature were determined based on hospital records or information obtained from a patient's family.

Statistical analysis

SACT in different clinical groups was presented as the mean ± standard deviation. A comparison between the groups was performed with Student's t-test or the non-parametric U Mann-Whitney test,

Table 1 Baseline clinical characteristics of sinoatrial conduction time (SACT) > 150 ms and SACT < 150 ms patients.

Variable	SACT > 150 ms (n = 35)	SACT < 150 ms (n = 183)	P
Age [years]	65.7 ± 9.4	53.1 ± 18.1	< 0.0001
Age > 60 years	29 (83%)	76 (42%)	< 0.0001
SACT [ms]	180.0 ± 25.0	85.0 ± 26.0	< 0.0001
Male sex	21 (60%)	95 (52%)	0.38
Structural heart disease:	30 (86%)	91 (49%)	< 0.0001
Hypertension	7 (20%)	48 (26%)	0.29
Coronary artery disease	21 (60%)	33 (18%)	< 0.0001
Valvular heart disease	2 (5.7%)	10 (5.4%)	0.6

as appropriate. Differences in categorical data were tested for statistical significance with the χ^2 test or Fisher's exact test, as appropriate. Pearson correlation was used to study the association between the variables. The relationship between the occurrence of events, such as a diagnosis of sinus node disease, a need for permanent pacing, or death regardless of its cause, and clinical variables (age, gender, structural heart disease, and SACT > 150 ms) was evaluated using the logarithmic rank test. Cox multivariate analysis was performed by accounting for clinical variables (age, gender, structural heart disease, and SACT > 150 ms) that were significantly correlated with the respective outcome in the univariate analysis ($p < 0.05$). To determine the most important independent variables influencing the outcome, results of the Wald test for individual parameter were examined, and the least significant variable that did not meet the level for staying in the model ($p < 0.05$) was removed in backward stepwise variable selection until the final analysis was reached. Statistical analysis was performed using the package Complete Statistical Systems (Microsoft Corporation, USA).

Results

The prospective follow-up duration of the study patients was 48 ± 11 months, the time to a diagnosis of sinus node disease was 26 ± 10 months, and the time to pacemaker implantation was 29 ± 8 months. During the observation, 17 patients died, including 8 (23%) with SACT > 150 ms and 9 (5%) with SACT < 150 ms. Sinus node disease was diagnosed in 22 patients, including 18 (51%) with SACT > 150 ms and 4 (2%) with SACT < 150 ms. Indications for pacemaker implantation were identified in 16 patients: 13 (37%) with SACT > 150 ms and 3 (2%) with SACT < 150 ms. Baseline clinical characteristics of patients with SACT values > 150 ms and < 150 ms is presented in Table 1 and the average values of SACT in different clinical groups in Table 2. Patients with SACT values > 150 ms were significantly older (65.7 ± ± 9.4 vs. 53.1 ± 18.1 years; SACT > 150 ms vs. < 150 ms group; respectively, $p < 0.0001$) and had markedly higher prevalence of coronary artery disease (60% vs. 18%, SACT > 150 ms vs. < 150 ms group; respectively, $p < 0.0001$).

Table 2. The average values of the baseline sinoatrial conduction time (SACT) in different clinical groups.

Clinical group	Average SACT [ms]	P
Sinus node disease (+)	175 ± 52	< 0.0001
Sinus node disease (–)	87 ± 34	
PM implantation (+)	178 ± 59	< 0.0001
PM implantation (–)	81 ± 38	
Age ≥ 60 years	156 ± 41	< 0.0001
Age < 60 years	72 ± 24	

Sinus node disease (+) — occurrence of sinus node disease during follow-up; PM implantation (+) — occurrence of indications for pacemaker implantation during follow-up

Univariate analysis showed a significant relationship between sinus node disease, pacemaker implantation and death and clinical variables, such as age, gender, structural heart disease, and SACT (Table 3). In the multivariate Cox analysis SACT values > 150 ms were independently associated with future diagnosis of sinus node disease (relative risk [RR] 48.3; $p < 0.0001$) and pacemaker implantation during follow-up (RR 36.4; $p < 0.0001$) (Table 4). The only significant predictor of death (overall mortality) during the prospective observation was age > 60 years (RR 12.8; $p = 0.014$).

Table 3. Relationship between the occurrence of sinus node disease, pacemaker implantation, and death (overall mortality) during the prospective observation and the following clinical variables: age, gender, structural heart disease, and baseline sinoatrial conduction time (SACT) value > 150 ms. The results of the univariate analysis are shown.

	Log-rank test	P
Sinus node disease		
Age > 60 years	4.2011	< 0.0001
Male gender	2.1535	0.04
Structural heart disease	4.6912	< 0.0001
SACT > 150 ms	5.9210	< 0.0001
Pacemaker implantation		
Age > 60 years	2.5604	0.016
Male gender	2.3930	0.032
Structural heart disease	3.6219	0.002
SACT > 150 ms	4.9921	< 0.0001
Death		
Age > 60 years	3.9821	0.005
Male gender	2.0011	0.04
Structural heart disease	3.6302	0.007
SACT > 150 ms	2.0109	0.04

Table 4. Final multivariate Cox regression models for events occurring during the follow-up: sinus node disease, pacemaker implantation and death. Entry variables are: age, gender, structural heart disease, and baseline sinoatrial conduction time (SACT) value > 150 ms.

	Wald test	P	RR (95% CI)
Sinus node disease (χ^2 = 82.3; p < 0.0001)			
Structural heart disease	3.61	0.057	3.9 (0.96–16.3)
SACT > 150 ms	37.5	< 0.0001	48.3 (13.9–166.9)
Pacemaker implantation (χ^2 = 88.4; p < 0.0001)			
Structural heart disease	5.63	0.018	7.4 (1.4–38.9)
SACT > 150 ms	42.38	< 0.0001	36.4 (12.3–107.3)
Death (χ^2 = 12.7; p = 0.0004)			
Age > 60 years	6.1	0.014	12.8 (1.7–96.9)

CI — confidence interval; RR — relative risk

Discussion

The results of our study indicate that during the average 4-year prospective follow-up of patients with unexplained syncope, the baseline SACT values above 150 ms were associated with significantly increased probability of sinus node disease and markedly higher need for permanent pacing. SACT values were not associated with the incidence of death (overall mortality).

During 24-h ECG Holter monitoring, the incidence of spontaneous APDs in a healthy population ranges in various studies from 12% to 87%. In the majority of middle-aged and older people referred to the Holter test, it is possible to calculate SACT due to the high incidence of APDs. The basis for an indirect method of SACT measurement is to compare the length of the first return cycle after APD with a basic sinus cycle length. The duration of the return cycle strictly depends on the conduction time into and out of the sinus node and on sinus automaticity. The difference between the first return cycle and sinus cycle length has been considered to be an estimate of total SACT [7]. Assuming that conduction time into and out of the sinus node is equal, half of the above-mentioned difference is considered as SACT. Studies comparing indirect methods of SACT measurement (both Strauss' and Narula') with directly recorded SACT have shown a good correlation of the results obtained from these methods in patients without and with sinus node dysfunction [8–10]. A comparison of SACT values derived from 24-h Holter monitoring with SACT estimated by the Strauss' method during invasive electrophysiological testing was also performed in our study in a series of 52 patients referred to electrophysiological testing as a part of a diagnostic work-up. The results from both methods are highly correlated (Fig. 2).

One of the most used techniques for assessing overall sinus node function is based on the determination of sinus node recovery time (SNRT) and its correction for the underlying sinus cycle length [7, 11]. Corrected SNRT (cSNRT) is a measure of the effect of overdrive pacing on both sinoatrial conduction and automaticity [12]. Although the prognostic value of a prolonged SNRT is not well established, the current guidelines determine its diagnostic role in patients with syncope, with no additional tests required, in sinus bradycardia and prolonged cSNRT > 525 ms in electrophysiological study [1]. The prognostic significance of SACT may not only refer to the prediction of a sinus node disease associated with paroxysmal or permanent sinoatrial blocks of II–III°. The results of tests carried out by the direct recording of sinus node potentials indicate that sinoatrial conduction disturbances may also cause an interruption of sinus rhythm, which is traditionally interpreted as a symptom of inhibition of sinus node automaticity, such as in patients with tachycardia-bradycardia syndrome or carotid sinus hypersensitivity. Asseman et al. [12] showed that prolonged SNRT after the cessation of rapid atrial pacing is more frequently caused by sinoatrial blocks than depressed automaticity of sinus pacing cells. Gang et al. [13] drew attention to the important role of disturbances of sinoatrial conduction in patients with carotid sinus hypersensitivity. Registering sinus node potentials during carotid sinus massage, these authors observed prolonged SACT directly before the appearance of asystole and sinoatrial block during asystole.

A limitation of the Holter method is the need to search for APDs eligible for SACT measurement. In ECG fragments with a regular sinus rhythm, a single measurement of SACT during daytime is reliable [2]. When there is little variability in the duration of the PP interval, making several measurements and calculating the average values of SACT are justified. However, in the event of significant arrhythmia, neither the Holter nor Strauss' method can be applied for SACT calculation [6]. The autonomic nervous system is probably the most potent extrinsic factor modulating sinoatral conduction. Patients with sinus node dysfunction and a history suggesting vasovagal syncope have increased vagal activity both at rest and during tilting, higher heart rate variability [14] and also significantly increased SACT variability [15]. Autonomic blockade reduces SACT by Strauss' method variability, which becomes comparable with SACT variability observed in healthy subjects. Graff et al. [15] showed that patients with sinus node dysfunction and no history suggesting vasovagal syncope present distinct electrophysiological features. They had significantly lower SACT variability at basal state and higher SNRT and cSNRT variabilities after autonomic blockade in comparison with patients who had experienced a vasovagal syncope. Regular sinus rhythm that is a prerequisite for SACT calculation in Holter monitoring, promotes this method in evaluation of patients with predominant organic dysfunction of sinus node. In our study careful anamnesis allowed to exclude patients with a typical history of vasovagal syncope, and moreover, Holter SACT values > 150 ms were obtained in patients 65.7 ± ± 9.4 years of age, with high prevalence of coronary artery disease (60%). Age and a structural heart disease are clinical conditions that coincide with reduced heart rate variability what undoubtedly facilitates the application of the Holter method in SACT calculation. On the other hand impaired sinoatrial conduction in this milieu may reflect mostly

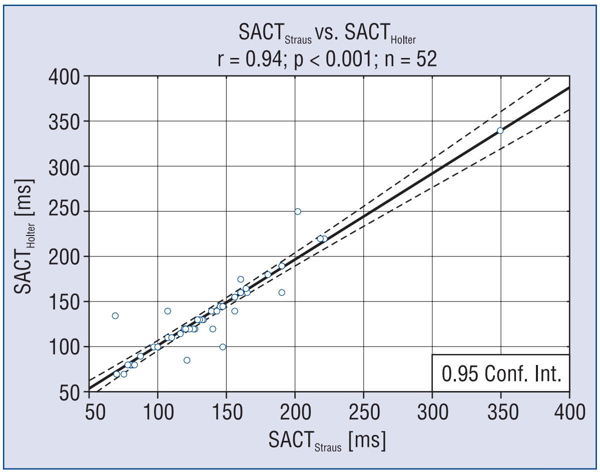

Figure 2. A comparison of the results of sinoatrial conduction time (SACT) calculation by the Straus method with SACT derived from Holter monitoring in 52 patients of the study population.

organic component of dysfunction. Reliability of the measurement and the nature of reflected abnormality in this population are probably crucial factors responsible for prognostic significance and a high correlation between SACT results obtained from Holter monitoring and Strauss' method (Fig. 2). Nevertheless, in order to minimize the significance of autonomic influence on SACT, measurements should be performed under standardized conditions during daytime [2], without the effect of medications or any other substance that could alter autonomic balance.

Another important issue for SACT estimation is related to the site of origin of spontaneous or induced APD [7]. In our study, only the Holter electrocardiograms with APDs of positive P wave direction in lead CM5 were selected. The morphology of the ECG recorded from this lead corresponds to the curve obtained from lead V_5 and also partly from the limb lead II of a standard ECG. It seems that in the absence of APDs with a positive P wave in lead CM5, for SACT measurement purposes, premature contraction with a negative P wave originating from the inferior right or left atrium can also be used. Differences in SACT values determined by the method of stimulation of the upper and lower parts of the right atrium and coronary sinus area do not exceed 20 ms [16].

Perspectives

This study may have clinical implications. As a noninvasive and easy to perform Holter SACT measurement may be used as a screening examination to select patients with unexplained syncope and abnormal SACT values (> 150 ms) for further invasive diagnostic work-up in order to apply effective therapeutic options, e.g. pacemaker implantation, without hazardous time delay.

Conclusions

The results of our study suggest that the Holter method of SACT calculation is useful in predicting the future occurrence of sinus node disease and the need for permanent pacing in patients with unexplained syncope.

Conflict of interest: none declared

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