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ORIGINAL ARTICLE

Heart rate variability in sick sinus syndrome: does it have a diagnostic role?

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ABSTRACT

BACKGROUND: Hypothesis of our study was that the irregular rhythm of sick sinus syndrome (SSS) was characterized by an augmented HRV. Objective was to assess whether SSS patients had a typical HRV profile.

METHODS: We screened all 1947 consecutive Holter ECGs performed in our Units of Vascular Medicine and Internal Medicine and Cardioangiology at the University of Palermo (Italy) from April 2010 to September 2014. Among these, we selected 30 patients with ECG criteria of SSS. They were compared to 30 patients without SSS matched for age, sex and comorbidities.

RESULTS: The SSS group had a lower mean heart rate (HR) (P=0.003), and a longer mean NN max-min longer (P<0.0005) compared to control group. SSS group had higher mean pNN50 (P=0.043), mean RMSSD (P=0.006), mean SDNN (P=0.021), and mean SDNNi (P=0.005) as compared with control group. Moreover, HR ≤64.5 bpm, NN max-min>1355 msec, pNN50>16.08, RMSSD>50.2, SDNN>151.94, and SDNNi>71.1 showed a predictive value for diagnosis of SSS. The positivity of all 6 variables according to the aforementioned cut-offs ensured a positive predictive value of 100% and the negativity of all 6 variables had a negative predictive value of 94% for diagnosis of SSS. Among SSS patients, we did not observe any correlation between HR and HRV variables.

CONCLUSIONS: SSS patients have a HRV profile characterized by: low HR, long NN max-min interval, and elevated pNN50, RMSSD, SDNN and SDNNi values with specific diagnostic cut-offs for diagnosis of SSS. Moreover, we found the absence of correlation between HR and all time-domain HRV variables in SSS patients.

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KEY WORDS: Sick sinus syndrome; Autonomic nervous system; Electrocardiography, ambulatory.

Sick sinus syndrome (SSS) is a collection of disorders defined by abnormal cardiac impulse formation and by abnormal propagation from the sinoatrial (SA) node to the atrial tissue, which prevents it from performing its pacemaking function. Patients with SSS may have an intrinsic or extrinsic abnormality of sinus node automaticity. Intrinsic causes of SSS include degenerative fibrosis of the SA node, infiltrative disease processes, ion channel dysfunction and remodeling of the SA node. Extrinsic factors that can mimic or exacerbate SSS include the use of certain pharmacologic agents, ischemia, toxins, obstructive sleep apnea, metabolic disturbances and autonomic dysfunction.[1]

Since the SA node and atrium are richly inner-

vated by both sympathetic and parasympathetic nerve fibres, the pacemaker cells are directly affected by the release of the acetylcholine and catecholamines.[2] Heart rate variability (HRV) is a reproducible non-invasive measure of the interaction between cardiac sympathetic and parasympathetic activity, which causes changes in cardiac cycle length.[3-5] Time-domain methods are ideal for the analysis of long-term recordings as, compared to short term analysis, they are more stable and are not influenced by confounding factors such as body position, physical activity, respiration, and environmental factors like temperature;[6] moreover, time-domain HRV is computationally more simple than frequency-domain HRV, it is more tolerant to data imperfections, and it involves none of the assumptions that underlie spectral analysis.[7]

Few studies evaluated characteristics and reliability of HRV in patients with SSS but their results were not univocal.[8-10]

Hypothesis of our study was that the irregular rhythm of SSS could be characterized by an augmented HRV. Thus, objective of our study was to elucidate the time domain analysis 24 hours (h) HRV profile of a group of patients with SSS (hypothesized as the group with a pathological augmentation of HRV) compared to a group of patients without SSS matched for age, sex and comorbidities.

Materials and methods

The study was carried out in accordance with the provisions of the Declaration of Helsinki and local regulations. Retrospectively, we screened all the 24h ambulatory electrocardiogram (ECG) recordings of patients referred to our Units of Vascular Medicine and Internal Medicine and Cardioangiology at the University of Palermo (Italy) for symptoms suggestive of arrhythmias (palpitations, fainting, near-fainting, dizziness, fatigue, weakness, confusion, chest pain, disturbed sleep) between April 2010 and September 2014.

We selected all patients with SSS among those screened. Diagnosis of SSS was made when any of the following ECG criteria were present: 1) persistent and severe (<45 bpm) diurnal sinus bradycardia; 2) SA exit block; 3) SA arrest with an escape atrial or junctional rhythm; 4) SA arrest with failure of subsidiary pacemaker; and 5) bradycardia-tachycardia syndrome.[11] Exclusion criteria were: patients with cardiac pacemaker or implantable cardiac device, insufficient recordings (recording duration <20h and/or non-sinus beats >25%), patients with sustained (>30 seconds) supraventricular or ventricular tachycardias and patients with escape rhythm longer than 3 minutes. All patients with less than 24h analyzable beats in the ECG recording had, nevertheless, data that included the whole night.

Comorbidities were evaluated on the basis of the following criteria. Hypertension was defined as present if subjects had been previously diagnosed according the World Health Organization/International Society of Hypertension guidelines and were routinely receiving antihypertensive therapy.[12] Patients were defined as diabetics if they had known diabetes mellitus treated by diet, oral hypoglycemic drugs or insulin. Patients were considered affected by coronary artery disease (CAD) if they had a previous acute myocardial infarction, a previous coronary stent or aorto-coronary by-pass implant or an angina pectoris history with positive stress test, myocardial scintigraphy or coronary angiography. A diagnosis of heart failure (HF) was retained in patients with typical symptoms and/or signs and LEVF<40% or LEVF≥40% plus elevated levels of natriuretic peptides and at least one additional criterion between relevant structural heart disease and diastolic dysfunction.[13] Chronic kidney disease (CKD) was diagnosed according to KDIGO guidelines criteria.[14] Chronic obstructive pulmonary disease (COPD) was defined as a post-bronchodilator FEV1/FVC less than 0.70 in any patient with typical symptoms (dyspnea, chronic cough or sputum production) and/or a history of exposure to risk factors.[15]

Holter ECG recordings were performed using 4 Sorin Spiderview Digital Holter Recorders and 1 software ELA Medical SyneScope version 3.10 running under Microsoft Windows. There were two types of Holter Recorders: a seven electrode three-channel system and a ten electrode twelve-lead system. The software had capabilities for arrhythmia and HRV analyses. However, before HRV analysis, for each case a preliminary analy-

sis was carried out by a trained cardiologist unaware of subjects' clinical data, who selected one or two channels with a better signal quality and carefully inspected the ECG to identify potential artifacts, ectopic beats, and arrhythmic events.

From the analysis were excluded: artifacts (such as missed beats caused by failure to detect the R peak and electrical noise), NN intervals (defined as the time intervals between two consecutive QRS complexes) corresponding to supraventricular or ventricular extrasystole coupling interval and compensatory pause, NN intervals corresponding to missed beats (>175% of mean NN and greater than 800 milliseconds) and pauses longer than 2500 milliseconds (ms). All NN intervals included in the analysis were comprised between adjacent QRS complexes resulting from sinus beats.

According to the joint position statement by the e-Cardiology ESC Working Group and the European Heart Rhythm Association co-endorsed by the Asia Pacific Heart Rhythm Society, time domain methods evaluated were: pNN50 (percent difference between two consecutive NN intervals over 50 ms), RMSSD (square root of the mean squared differences of successive NN intervals), SDNN (standard deviation of all the NN intervals), SDNNi (corresponding to the mean standard deviation, each standard deviation being calculated over 5 minutes), and SDANN (standard deviation of the mean of the NN intervals, each mean being calculated over 5 minutes).[16] We used only data deriving from direct measurements of NN intervals. Moreover, we evaluated mean heart rate (HR) and the difference between the longest and the shortest NN interval (NN max-min), a simple and quick method to assess variability of NN intervals in 24h.

Statistical analysis

Statistical analysis of quantitative and qualitative data, including descriptive statistics, was performed for all items. Continuous data are expressed as mean±SD (standard deviation), unless otherwise specified. Baseline differences between groups were assessed by the Chi-square test or Fisher Exact test, as needed for categorical variables, and by the independent Student's *t*-test for continuous parameters. Correlation between continuous variables was tested using Pearson's correlation test. Data were analyzed by the Epi Info software (version 6.0, Centers for Disease Control and Prevention, Atlanta, GA, USA) and SPSS Software (version 21.0, SPSS Inc, Chicago, IL, USA). All P values were two-sided and P-values less than 0.05 were considered statistically significant. To assess the predictive role towards SSS diagnosis of different cut-off values of HR, NN max-min and HRV time-domain methods, a receiver operating characteristic (ROC) curve with calculations of area under the curve and 95% confidence intervals (CIs) was constructed and sensitivity and specificity values were calculated. Sensitivity was defined as the percentage of patients with a positive test on the total of SSS patients. Specificity was defined as the percentage of patients with a negative test on the total of control patients. Positive predictive value was defined as the percentage of SSS patients on the total of patients displaying a positive test. Negative predictive value was defined as the percentage of control patients on the total of patients displaying a negative test.

Results

From April 2010 to September 2014, 1947 patients were referred to our Holter Centers of Vascular Medicine and Internal Medicine and Cardioangiology Units at the University of Palermo (Italy) for 24h ambulatory ECG recording. Overall, 54 patients had a diagnosis of SSS ac-

TABLE I.—*Clinical characteristics of patients with sick sinus syndrome and control group.*

	SSS	Control group	P
N.	30	30	-
Age (years)	74±9.9	72±9.9	0.621^
Sex (M/F)	9/21	9/21	1.0*
Hypertension	23 (77%)	24 (80%)	1.0*
Diabetes mellitus	8 (27%)	9 (30%)	1.0*
CAD	6 (20%)	7 (23%)	1.0*
Heart failure	9 (30%)	7 (23%)	0.771*
CKD	7 (23%)	9 (30%)	0.771*
COPD	4 (13%)	5 (17%)	1.0*

Data expressed as mean±SD, or number of patients with the characteristic (%).
SSS: sick sinus syndrome; CAD: coronary artery disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease.
^Student's *t*-test; *Chi-square test or Fisher Exact test, as needed.

TABLE II.—*Heart rate variability 24h analyses in time domain in patients with SSS and in control group.*

	SSS group	Control group	P	
Age (years)	74±9.9	72±9.9	0.621	
HR (bpm)	61.8±9.5	69.6±9.6	0.003	
NN max-min (ms)	2137.3±1031.5	950.2±247.4	<0.0005	
pNN50 (%)	27.4±24	11.2±14.8	0.002	0.043*
RMSSD (ms)	117±111.3	46.8±38.4	<0.0005	0.006*
SDNN (ms)	159.6±70.4	111.5±29.2	0.001	0.021*
SDNNi (ms)	101±70.3	54.8±25.4	<0.0005	0.005*
SDANN (ms)	113.7±35.5	92.1±28.6	0.05	0.468*

Data expressed as mean±SD.
SSS: sick sinus syndrome; HR: heart rate; 24h: 24 hours; NN max-min: difference between the longest and the shortest NN interval; pNN50: percentage of differences between adjacent NN intervals>50 ms; RMSSD: root mean square of successive differences of adjacent NN intervals; SDNN: SD of the NN intervals; SDNNi: mean of the SD of NN intervals calculated in 5-min segments; SDANN: SD of the averages of the NN intervals calculated in 5-min segments; bpm: beats per minute; ms: milliseconds; *data corrected for heart rate.

cording to the previous described criteria and, among these, 30 did not show the exclusion criteria. Among 30 pure selected patients, 9 were male and 21 were female and the mean age was 74 years (Table I). They were compared to 30 patients without SSS matched for age, sex and comorbidities (Table I). The SSS group had a lower mean HR 24h (P=0.003), and a higher mean NN max-min (P<0.0005), mean pNN50 (P=0.043), mean RMSSD (P=0.006), mean SDNN (P=0.021), and mean SDNNi (P=0.005) compared to control group (Table II).

In order to evaluate the diagnostic power of all variables with significant between-group differences, we assessed the predictive role of different cut-off values for SSS diagnosis at ROC curve analysis: a HR ≤64.5bpm (sensitivity: 63.3% – specificity: 73.3%), a NN max-min>1355 msec (sensitivity: 93.3% – specificity: 93.3%), a pNN50>16.08 (sensitivity: 60% – specificity: 83.3%), a RMSSD>50.2 (sensitivity: 66.7% – specificity: 76.7%), a SDNN>151.94 (sensitivity: 43.3% – specificity: 96.7%), and a SDNNi>71.1 (sensitivity: 56.7% – specificity: 90%), which showed a significant predictive value with an area under ROC curve of 71.7%, 97.1%, 73.4%, 75.1%, 69.9%, and 73%, respectively (Table III). The positivity of all 6 variables according to the aforementioned cut-offs ensured a positive predictive value of 100% (sensitivity 30% - specificity 100%) and the negativity of all 6 variables had a negative predictive value of 94% (sensitivity 97% - specificity 57%) for diagnosis of SSS.

Among SSS patients, we did not observe a significant correlation between HR and HRV variables. On the contrary, in control group HR had a significant correlation with pNN50 (P=0.014) and SDNNi (P=0.021) (Table IV).

Discussion

Our study found that patients with SSS had an altered time-domain HRV profile in comparison to a control group matched for age, sex and comorbidities.

TABLE III.—*ROC curves analysis of HR, NN max-min and positive time-domain HRV variables with predictive diagnostic role of different cut-off values for SSS diagnosis.*

Variables	Cut-off	Sensibility	Specificity	Area under ROC curve	95% CI	P
HR	≤64.5 bpm	63.3	73.3	0.717	0.586-0.826	0.0011
NNmax-min	>1355*	93.3	93.3	0.971	0.891-0.997	<0.0005
pNN50	>16.08	60	83.3	0.734	0.605-0.840	<0.0005
RMSSD	>50.2	66.7	76.7	0.751	0.623-0.854	<0.0005
SDNN	>151.94	43.3	96.7	0.699	0.567-0.811	0.0035
SDNNi	>71.1	56.7	90	0.730	0.600-0.837	0.0005

bpm: beats per minute; *milliseconds.

TABLE IV.—*Correlation analysis between heart rate and complex time-domain HRV variables in 24 hours for both groups of patients.*

	Heart rate			
	Sick sinus syndrome		Control group	
	Pearson's correlation coefficient	P	Pearson's correlation coefficient	P
pNN50	-0.90	0.635	-0.444	0.014
RMSSD	-0.94	0.622	-0.356	0.054
SDNNi	-0.74	0.696	-0.419	0.021
SDANN	-0.209	0.267	-0.188	0.319
SDNN	-0.127	0.502	-0.319	0.086

pNN50: percentage of differences between adjacent NN intervals>50 ms; RMSSD: root mean square of successive differences of adjacent NN intervals; SDNN: SD of the NN intervals; SDNNi: mean of the SD of NN intervals calculated in 5-min segments; SDANN: SD of the averages of the NN intervals calculated in 5-min segments.

At Holter monitoring, SSS patients had a lower mean HR than control group. Severe and symptomatic sinus bradycardia can be the initial manifestation on standard ECG of an intrinsic SSS.[17, 18] The mechanism of bradycardia in SSS may be either disordered impulse generation within the sinus node or impaired conduction of impulses from the sinus node into the atrium.[17] Therefore, sinus bradycardia is common but is not typical for SSS. Indeed, it could be observed overnight in normal subjects exhibiting an increased parasympathetic tone (juveniles, athletes, and so forth).[18] Moreover, it can be simulated by other conditions which do not directly involve the sinus node, such as a blocked bigeminal premature atrial beat hidden in the T wave of the sinus beat.[18]

In our study, SSS group had a mean NN max-min longer than control group. The reason is that patients with SSS, having SA exit blocks, sinus arrests or severe sinus bradycardia, had a long NN max interval; moreover, in about 50% of cases of SSS, bradycardias are accompanied by rapid heart rhythms, referred to as tachycardia-bradycardia syndrome.[1] Therefore, NN max-min interval is frequently long in these patients.

As far as time domain HRV variables are concerned, in our study, patients with SSS showed an increased mean pNN50, mean RMSSD, mean SDNN, and mean SDNNi compared to matched group.

Globally, few studies have investigated HRV profile in SSS patients with not univocal findings using different HRV measurements. In a study, Poincaré plots and power spectral analysis were applied to short-term variations of sinus cycles in a group of patients with SSS, showing three patterns of behavior: completely normal, random-like pattern and transitional pattern.[10] Two studies have shown an elevated HRV in patients with SSS using the range of variation of sinus cycle length (SCL) standardized by dividing by mean SCL and the maximal change in SCL between any two consecutive cycles in short (about 1 minute) continuous ECG recordings.[8, 19] Finally, Shin DG *et al.* showed an inappropriate reduction of intermediate-term fractal scaling exponent in SSS patients, calculated in 60 minutes sinus RR interval data of sinus bradycardia from 24h ambulatory ECGs.[9]

The main findings of our study are the diagnostic cut-offs for all variables with significant between-group differences. The medical diagnosis for SSS is complex and involves tying together both ECG signs and physical symptoms (lightheadedness, syncope, fatigue, palpitations). It accounts for approximately 30% to 50% of all the pacemaker implants in the United States.[20] Although sometimes the diagnosis is easy, certain and unequivocal, there is a whole range of clinical situations where it is subtle and much more difficult; in these cases, invasive investigations such as an implantable loop recorder or an electrophysiological study can be considered. However, in these doubtful cases, before subjecting a patient to invasive investigations, in addition to medical history, a simple Holter evaluation of HRV could direct the iter diagnostic. In our study, a HR ≤64.5 bpm, a NN max-min>1355 msec, a pNN50>16.08, a RMSSD>50.2, a SDNN>151.94, and a SDNNi>71.1 had a predictive value for diagnosis of SSS. These diagnostic cut-offs were more specific (all values over 70%) than sensible, except for a NN max-min interval>1355 msec, whom showed the highest diagnostic power with both a sensitivity and a specificity equal to 93.3%. The positivity of all 6 variables according to the aforementioned cut-offs ensured a positive predictive value of 100% (sensitivity 30% - specificity 100%) and the negativity of all 6 variables had a negative predictive

TABLE V.—*Standard electrocardiographic presentations and time-domain HRV profile of SSS in accordance with our study.*

Standard electrocardiographic presentations of SSS[11]	Time-domain HRV 24h profile of SSS
1) Severe sinus bradycardia	1) Low HR
2) Sino-atrial block	2) Long NN max-min interval
3) Sino-atrial arrest with an escape atrial or junctional rhythm	3) Elevated pNN50, RMSSD, SDNN and SDNNi
4) Sino-atrial arrest with failure of subsidiary pacemaker	4) Absence of correlation between HR and all time-domain HRV variables
5) Bradycardia alternating with tachycardia	

SSS: sick sinus syndrome; HRV: heart rate variability; 24h: 24 hours; HR: heart rate; NN max-min: difference between the longest and the shortest NN interval; pNN50: percentage of differences between adjacent NN intervals >50 ms; RMSSD: root mean square of successive differences of adjacent NN intervals; SDNN: SD of the NN intervals; SDNNi: mean of the SD of NN intervals calculated in 5-min segments.

value of 94% (sensitivity 97% - specificity 57%) for diagnosis of SSS.

Finally, in our study, we found a significant correlation between HR and pNN50 and SDNNi in the control group and no correlation between HR and all the HRV variables in SSS group.

A good correlation between mean HR and time domain measures of HRV on 24h ambulatory ECGs was demonstrated in healthy subjects.[21] However, other studies showed that with the aging or comorbidities such as CAD or HF, the relationship between HR and HRV weakens.[22-25] Our findings are consistent with those presented in a study by Sosnowski *et al.*,[8] that found an inverse relationship or a lack of correlation between HR and other HRV measurements in patients older than 50 years with SSS. Therefore, the absence of correlation between HR and all the complex time-domain HRV variables seems to be another characteristic of SSS.

In summary, Table V[11] shows standard ECG presentations and time-domain HRV profile of SSS according to our study. Further studies on larger populations are necessary to confirm our findings.

Limitations of this study

Possible limitations of our study are: the retrospective nature of the study, the relatively short size of the enrolled patients, and the erratic course of SSS that sometimes shows periods of normal node function alternating with abnormal behavior; however, they are consistent with other studies on the topic. Moreover, even if the incidence of SSS increases with aging, it can occur at any age and it has been observed in newborns too.[20] However, SSS patients in our study had a mean age of 74±9.9 years, therefore the diagnostic cut-offs found in our study could not be applied to young patients, who could have an augmented HRV as a reflex of physiological respiratory sinus arrhythmia.

Conclusions

In conclusion, our study found that patients affected by SSS have, at Holter monitoring, a HRV profile characterized by: low HR, long NN max-min interval, and elevated pNN50, RMSSD, SDNN and SDNNi values as compared with age and comorbidities matched patients. For all these variables, cut-offs for diagnosis of SSS were identified. Moreover, we observed the absence of correlation between HR and all the time-domain HRV variables in these patients.

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