

Electrophysiological features in patients with sinus node dysfunction and vasovagal syncope

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Abstract

Introduction: Syncope is a common presentation of sinus node dysfunction (SND). Some patients who receive a permanent pacemaker due to SND do not benefit from it and further diagnostic workup leads to the diagnosis of vasovagal syncope (VVS). The aim of the study was to identify electrophysiological criteria that can be used for identification of patients with SND and concurrent VVS.

Material and methods: Transoesophageal atrial pacing (TAP) was performed in 100 patients divided into four groups depending on symptoms and TAP results. Standard electrophysiological parameters of sinus node function and their variability were obtained in the basal state and after pharmacological autonomic blockade (AB).

Results: Patients with concurrent SND and VVS had a greater variability of sinoatrial conduction time assessed by Strauss' method than patients without incidents of syncope (83.2 ± 53.9 vs. 34.1 ± 19.6 , 47.8 ± 33.6 and 32.1 ± 22.99). Apart from abnormal sinus node recovery time and second pause, patients with SND had bigger basal state variability of these parameters. In patients with SND and concurrent vasovagal syncope the variability of sinus node recovery time (SNRT), corrected SNRT (cSNRT) and second pause (IIP) decreased after autonomic blockade.

Conclusions: Patients with concurrent SND and VVS have distinct electrophysiological features – greater sinoatrial conduction time (SACT) variability and the decrease of SNRT, cSNRT and IIP variability after AB. However, further studies in larger study groups are needed to validate our findings. Transoesophageal atrial pacing is a useful procedure in patients with syncope, especially when the coexistence of more than one cardiac cause is suspected.

Key words: syncope, sinus node dysfunction, vasovagal syncope, transoesophageal atrial pacing, sinoatrial conduction time variability.

Introduction

Syncope is a common presentation of sinus node dysfunction. However, there are no exact values of electrophysiological parameters which can be useful to discriminate whether sinus node dysfunction is the cause of syncope. The sensitivity of sinus node recovery time (SNRT) or corrected

SNRT (cSNRT) is limited, although marked prolongation of SNRT/cSNRT increases the possibility that sinus node dysfunction may be responsible for syncope [1]. Sinoatrial conduction time (SACT) assessment is not recognized as a diagnostic tool for syncope [2]. It is known that some patients who receive permanent pacemakers due to sinus node dysfunction (SND) do not benefit from it and have syncope recurrences [3]. In some such cases further diagnostic workup leads to the diagnosis of vasovagal syncope (VVS). On the other hand, the only commonly used test for diagnosing vasovagal syncope, the head-up tilt test (HUTT), has many limitations [4]. Moreover, the mechanism of syncope in patients without organic heart disease does not correlate with findings during HUTT [5, 6].

The aim of the present study was to identify electrophysiological criteria that can be used to identify patients with sinus node dysfunction and concurrent vasovagal syncope.

Material and methods

Patients

Transoesophageal atrial pacing (TAP) was performed in 100 patients. The study group was divided into four groups depending on symptoms and results of TAP:

- group 1: patients with SND and a history suggesting VVS,
- group 2: patients with SND with no previous syncope,
- group 3: patients without SND but with a history suggesting VVS,
- group 4: patients without SND and without a history suggesting VVS.

We used the following diagnostic criteria for sinus node dysfunction:

- clinical features: syncope or presyncope, dizziness, shortness of breath, fatigue, blurred vision, memory loss, chest pain, palpitations [7],

- electrocardiographic features: sinus bradycardia < 50/min, sinus pause > 2 s, sinoatrial exit block [7],
- electrophysiological criteria: corrected sinus node recovery time (cSNRT) > 525 ms and/or sinoatrial conduction time by Strauss' method (SACT St) > 200 ms and/or intrinsic heart rate (IHR) lower than predicted [8, 9].

The following history findings suggested vasovagal syncope [2]:

- triggers of syncope: prolonged standing, warm environment, injections, sight of blood or syringes, pain, stressful situations,
- concurrent symptoms: diaphoresis, dyspnoea,
- short duration of syncope episodes,
- incidence characteristic: occurrence of different types of syncope suggesting more than one cause of incidents.

Inclusion criteria:

- diagnostic TAP in patients with or without a history of syncope,
- age over 18 years.

Exclusion criteria:

- inability to safely discontinue medications which could affect electrophysiological properties of the heart, for at least 5 half-lives prior to TAP (at least 3 months in case of amiodarone),
- contraindications to drugs used in the TAP protocol,
- heart rhythm other than sinus rhythm at the beginning of TAP and HUTT.

The patients had no symptoms of heart, renal, respiratory or hepatic failure. Patients with complex ventricular arrhythmias were not included in the study. The prevalence of coronary artery disease, hypertension and diabetes as well as incidence of syncope and palpitations are shown in Table I. In group 4 there were 3 patients with a history of a single syncope due to an overdose of antihypertensive drugs. They all had a negative HUTT.

Table I. Patients' characteristics

Parameter	Group 1	Group 2	Group 3	Group 4
Number of patients	16	24	32	28
Age [years]:				
Mean	45.9	63.8	43.3	52.1
Standard deviation	21.0	15.9	18.6	18.6
Median (min-max)	49 (18-84)	67.5 (26-90)	44.5 (18-76)	49.5 (18-90)
Gender: females/males	10/6	18/6	23/9	18/10
Coronary artery disease, n (%)	2 (12.5%)	1 (4.2%)	5 (15.6%)	2 (7.1%)
Hypertension, n (%)	2 (12.5%)	1 (4.2%)	4 (12.5%)	5 (17.9%)
Diabetes, n (%)	0 (0%)	0 (0%)	1 (3.1%)	1 (3.6%)
Syncope, n (%)	16 (100%)	0 (0%)	32 (100%)	3 (10.1%)
Palpitations as chief complaint, n (%)	2 (12.5%)	4 (16.7%)	14 (43.8%)	18 (64.3%)

Study protocol

The study complies with the Declaration of Helsinki; the protocol of the study was approved by the locally appointed ethics committee. Informed consent was obtained from each patient.

Head-up tilt test was performed in all patients with previous syncope [10]. The test was performed between 8 and 11 am, after an overnight fast. The patient remained supine for 20 min and then the table was tilted to 60°. An active test with 400 µg of nitroglycerine (aerosol, sublingually) was then performed. Passive test lasted 30 min; active test lasted 20 min, or until syncope occurred. In case of contraindications to NTG, a 45 min passive test was performed. The results were interpreted according to 2009 ESC guidelines on management of syncope [2].

Transoesophageal electrophysiological testing was performed in 100 patients [11, 12]. The combination of midazolam and fentanyl was administered to alleviate discomfort related to stimulation. This combination of drugs is safe and does not affect the sinus node function, atrioventricular conduction or the inducibility of tachycardia [13-15].

EDP-1 type 8-point electrodes and a programmable stimulator SP-5 plus (OBREAM – Zabrze, Poland) were used. The Fisher-Bloom EP System and Easy View Plus software (Prosmed, Poland) for personal computer were used for recordings. Pulses of 5 ms width and amplitude up to 20 mA were delivered. We obtained: SNRT, cSNRT, second pause (IIP), sinoatrial conduction time assessed by Strauss' (SACT St) and Narula's (SACT N) methods and the Wenckebach point (WP).

All the parameters were also assessed after pharmacological autonomic blockade (AB) with propranolol (0.1 mg/kg) and atropine (0.02 mg/kg) administered slowly intravenously following the protocol by Wallin [16]. The above protocol is considered safe and efficient in producing a complete autonomic blockade.

Intrinsic heart rate (IHR) was the heart rate recorded after the pharmacological autonomic denervation. Predicted IHR (IHRp) is age-appropriate IHR which is obtained using the formula: $IHRp = 118.1 \times (0.57 - \text{age [years]})$ [17]. An abnormal value of IHR was defined when it was lower than age predicted by more than 10%.

Sinoatrial conduction time was evaluated by Narula's method using 8 impulses with the rate slightly faster than the basic cycle length (BCL + 10/min) and repeated 3 times [18]. Sinoatrial conduction time was also assessed by the atrial extrastimulus technique [19]. Every eighth sinus cycle (A1 – A1) an extrastimulus (A2) was delivered and the return cycle (A2 – A3) was measured. We used 10 ms decrements until reaching atrial refractoriness. To obtain SACT by Strauss' method the

response of sinus node in so-called Zone II [(A1-A3) < 2(A1-A1)] was considered and the measurements from 1/3 external part of zone II were used.

Sinoatrial conduction time was estimated using the formula: $SACT\ St = 1/2 [(A2 - A3) - (A1 - A1)]$. Sinoatrial conduction time variability was assessed using the following methods:

method (1): SACT max – SACT min,

method (2): (SACT max – SACT min)/SACT max, (SACT max and SACT min are maximal and minimal values of SACT).

For SNRT, cSNRT and IIP the variability was defined as the difference between maximal and minimal values of the above parameters.

Statistical analysis

Data are presented as mean ± SD or percentage as appropriate. Comparison within a group was performed with Student's *t* test or Mann-Whitney *U* test. Comparisons between groups were performed by analysis of variance and post-hoc tests. Statistical significance was established at a value of $p < 0.05$. All analyses were performed using STATISTICA, version 7.1 (StatSoft, Inc).

Results

Head-up tilt test

Group 1: HUTT was positive in 75% of patients (in 12 out of 16 pts), the pattern being mixed (VASIS type 1) in 8 (66.7%), cardioinhibitory (VASIS type 2) in 3 (25%), and vasodepressor (VASIS type 3) in 1 (8.3%).

Group 3: HUTT was positive in 65.6% of patients (in 21 out of 32 pts), the pattern being mixed (VASIS type 1) in 14 (66.7%), cardioinhibitory (VASIS type 2) in 4 (19%), and vasodepressor (VASIS type 3) in 3 (14.3%) patients.

Transoesophageal atrial pacing

Transoesophageal atrial pacing was performed in 100 patients. There were no complications. Sinus node recovery time, cSNRT and IIP were successfully obtained in all patients. Sinoatrial conduction time assessed by Narula's method in the basal state was acquired in all patients but it was impossible to assess SACT N after AB in 6% of patients because of the irregularity of sinus rhythm (in 2 subjects), single premature ventricular or supraventricular beats (3 subjects) and the onset of atrial fibrillation before the completion of the study (1 subject). Sinoatrial conduction time assessed by Strauss' in the basal state was obtained in 89% and after AB in 87% of patients. Reasons for missing data were lack of so-called Zone II in 4 patients, numerous supraventricular beats in 6 patients, runs

of AV junctional rhythm in 2 patients and temporary malfunction of the recording device in two subjects.

Standard parameters

The values of SNRT, cSNRT, IIP, SACT N and SACT St are shown in Table II. After AB, patients in group 1 had significantly shorter SNRT, cSNRT and IIP compared to patients in group 2, while there were no significant differences between patients in groups 1 and 2 concerning SNRT and cSNRT in the basal state. Patients in group 1 also had shorter SACT N and SACT St but the difference was significant only with regard to SACT N. Mean cSNRT, SACT N and SACT St values in group 1 patients shortened after AB and were not significantly different than in groups without SND (3 and 4). All significant differences and the respective *p*-values are shown in Table II.

Intrinsic heart rate

The values of intrinsic heart rate were 80 ± 11 , 70 ± 11 , 91 ± 12 and 90 ± 15 /min in groups 1 to 4, respectively. Intrinsic heart rate values were significantly different in group 1 compared to all the other groups (group 1 vs. 2: *p* = 0.016; 1 vs. 3: *p* = 0.003; 1 vs. 4: *p* = 0.020). Abnormal values of IHR were found in 50% of patients in group 1 and 54% in group 2.

Sinoatrial conduction time variability

In patients with SND and VVS (group 1) SACT St variability was significantly different compared to other groups (Table III). After AB the differences disappeared with the exception of SACT St variability

as determined by method (2): (SACT max – SACT min)/SACT max (comparing groups 1 and 2). For method (1): SACT max – SACT min, there was an insignificant trend for greater SACT St variability in group 1 (*p* = 0.068).

The SACT N variability in patients in group 1 was not different from SACT N variability in patients in other groups. Groups with positive (A) or negative (B) responses to HUTT (3A vs. 3B and 1A + 3A vs. 1B + 3B) did not differ with regard to SACT variability.

SNRT, cSNRT and IIP variability

In the basal state, the SNRT, cSNRT and IIP variability in patients in group 1 was not different compared to group 2, but there was a significant difference between group 1 patients and patients without SND (group 3 as well as group 4). After AB, the variability of SNRT and cSNRT in group 1 was similar to groups 3 and 4 and significantly different only from group 2. Patients in group 1 had significantly different IIP variability compared to all other patients (Figures 1-3).

Wenckebach point

In the basal state the values of Wenckebach point were 134 ± 42 , 163 ± 33 , 156 ± 27 and 174 ± 28 /min in groups 1 to 4, respectively. After autonomic blockade they were 148 ± 31 , 165 ± 26 , 166 ± 21 and 175 ± 26 /min in groups 1 to 4, respectively.

Patients in group 1 had a lower WP than patients in group 4 (*p* = 0.003 in the basal state and *p* = 0.004 after AB). There were no statistically significant differences between group 1 and 2 or 3. After correction for age, abnormal WP was found in 6 (37.5%), 3 (12.5%), 9 (28 %) and 1 (3.6%) patient

Table II. Values of SNRT, cSNRT, IIP, SACT N and SACT St and comparison of standard parameters in groups 1-4

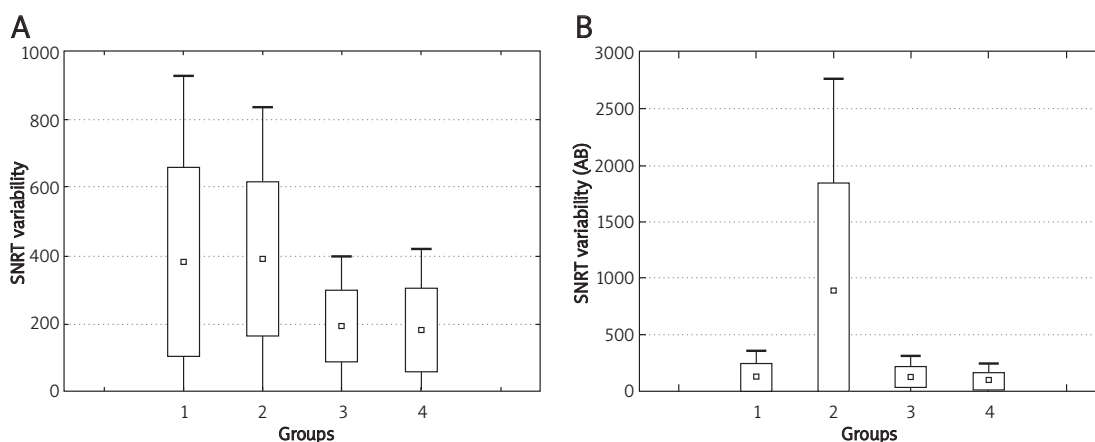
Sinus node parameters [ms]	Group 1	Group 2	Group 3	Group 4	Group 1 vs. 2 Value of <i>p</i>	Group 1 vs. 3 Value of <i>p</i>	Group 1 vs. 4 Value of <i>p</i>
Basal state							
SNRT	1579 ±578	1652 ±310	1151 ±213	1178 ±242	NS	0.0001	0.0011
cSNRT	613 ±412	641 ±204	355 ±95	345 ±101	NS	< 0.0001	0.0002
IIP	1363 ±321	1421 ±288	927 ±279	1009 ±285	NS	< 0.0001	0.0005
SACT N	259 ±87	236 ±63	208 ±63	191 ±36	NS	0.0171	0.0101
SACT St	193 ±42	187 ±53	163 ±35	166 ±30	NS	0.0212	0.0456
Autonomic blockade							
SNRT	1217 ±354	2185 ±957	953 ±168	948 ±197	< 0.0001	0.0069	0.0090
cSNRT	417 ±261	1202 ±890	276 ±84	267 ±84	< 0.0001	NS	NS
IIP	1002 ±295	1748 ±913	744 ±133	768 ±199	0.0002	0.0019	0.0090
SACT N	153 ±67	222 ±115	126 ±29	122 ±44	0.0180	NS	NS
SACT St	130 ±49	179 ±65	118 ±23	121 ±23	NS	NS	NS

SNRT – sinus node recovery time, cSNRT – corrected sinus node recovery time, IIP – second pause, SACT N – sinoatrial conduction time by Narula's method, SACT St – sinoatrial conduction time by Strauss' method, NS – non-significant

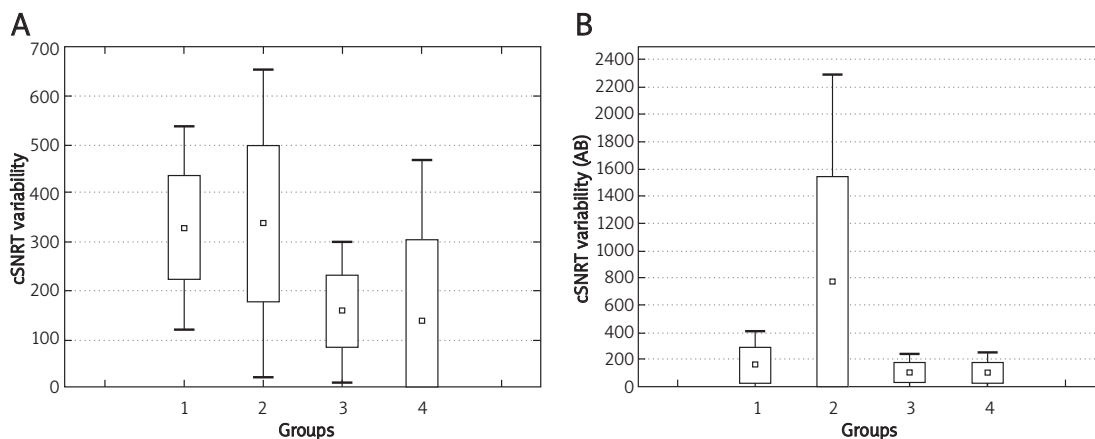
Table III. Sinoatrial conduction time by Strauss' method (SACT St) variability in groups 1-4

Method	Basal state		Autonomic blockade		Basal state		Autonomic blockade		Basal state		Autonomic blockade	
	Group 1 vs. 2				Group 1 vs. 3				Group 1 vs. 4			
	1	2	1	2	1	3	1	3	1	4	1	4
1	83.2 ±53.9	35.1 ±19.6	NS (<i>p</i> = 0.068)		83.2 ±53.9	47.8 ±33.6	NS		83.2 ±53.9	32.1 ±22.99	NS	
	<i>p</i> = 0.004		<i>p</i> = 0.0291				<i>p</i> = 0.0009					
2	0.42 ±0.22	0.20 ±0.10	0.10 ±0.10	0.07 ±0.04	0.42 ±0.22	0.28 ±0.16	NS		0.42 ±0.22	0.19 ±0.11	NS	
	<i>p</i> = 0.0031		<i>p</i> = 0.0017		<i>p</i> = 0.0391		<i>p</i> = 0.0017					

Method (1): SACT max – SACT min, method (2): (SACT max – SACT min)/SACT max, group 1: SND(+) VVS(+), group 2: SND(+), group 3: VVS (+), group 4: SND(-) VVS (-), NS – non-significant

**Figure 1.** Sinus node recovery time (SNRT) variability in groups 1-4 in the basal state (A) and after autonomic blockade (B)

Group 1: SND(+) VVS(+), group 2: SND(+), group 3: VVS (+), group 4: SND(-) VVS (-)

**Figure 2.** Corrected sinus node recovery time (cSNRT) variability in groups 1-4 in the basal state (A) and after autonomic blockade (B)

Group 1: SND(+) VVS(+), group 2: SND(+), group 3: VVS (+), group 4: SND(-) VVS (-)

in groups 1 to 4, respectively. Autonomic blockade decreased the number of patients with abnormal WP, especially in patients with VVS. After AB, Wenckebach point below the normal range was found in 5 (31.3%), 1 (4.2%), 2 (6.3%) and 1 (3.6%) patient in groups 1 to 4, respectively.

Discussion

In 1972 Mandel *et al.* described sinus node recovery time as a new method of assessing sinus node function [20]. After many years the prognostic value of SNRT is still not well defined. Menozzi *et al.* presented a prospective study in which patients

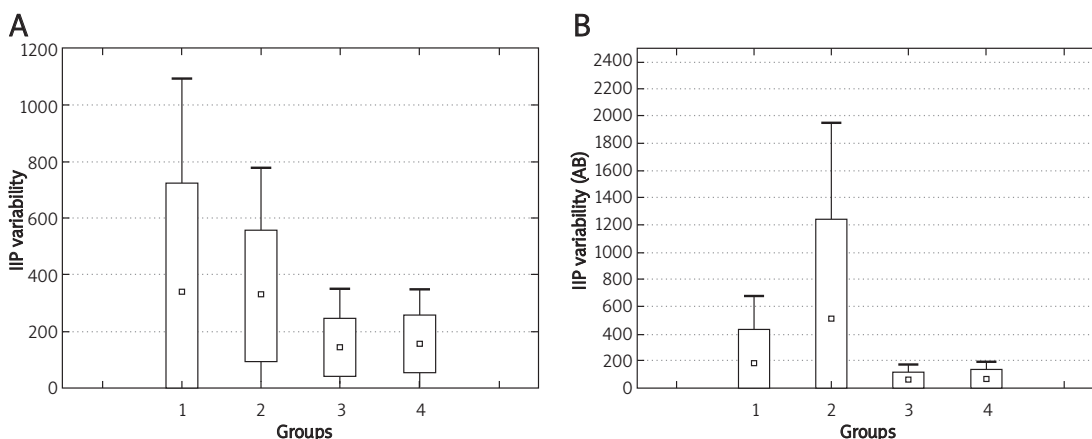


Figure 3. Second pause (IIP) variability in groups 1-4 in the basal state (A) and after autonomic blockade (B)
Group 1: SND(+) VVS(+), group 2: SND(+), group 3: VVS (+), group 4: SND(-) VVS (-)

with cSNRT > 800 ms had an eight times higher risk of having syncope than patients with cSNRTs below this value, but there are no more prospective data on this subject [1]. According to the last ESC Guidelines, prolonged cSNRT > 525 is diagnostic and indicates SND as a cause of syncope [2].

In our study, the basal state values of cSNRT in both groups with SND (1 and 2) were longer than reported by Alboni *et al.* [21]. After AB, the values of cSNRT in group 1 were similar and longer in group 2 patients than in the study cited above.

There were no differences between groups 1 and 2 (with and without syncope) with regard to SNRT, cSNRT and IIP in the basal state. Surprisingly, after AB all these parameters were significantly longer in patients without syncope. Abnormal IHR was found in 50% of patients in group 1 and 54% in group 2, so the percentage of intrinsic dysfunction in both groups was the same and cannot be an explanation for different reaction to AB. It appears that patients in group 1 had increased vagal stimulation at the basal state, which is in accordance with the data from heart rate variability analysis in vasovagal patients [22].

There are other studies which also suggest that autonomic modulation plays a crucial role in revealing syncope in patients with SND. Alboni *et al.* compared two groups of patients with sinus bradycardia less than 50/min [23]. As in our study, cSNRT was not different in patients with a history of syncope and patients without syncope. Patients with incidents of syncope had an abnormal IHR more often (in 66%) and patients without syncope less often (26%) than in our study. Brignole *et al.* studied 35 patients with SND and incidents of syncope [24]. Fifty-four percent of patients had a positive result of HUTT and in 80% either HUTT or carotid sinus massage (CSM) were positive. The results were independent of the presence of intrinsic SND or the severity of bradycardia. The authors suggested that an abnormal neural reflex is essential in the development of syncope in SND. This is also

supported by reports of results of various ablation procedures on sinus node function in patients treated for tachyarrhythmias [25, 26] and “cardioneuroablation” in patients with reflex syncope, functional atrioventricular block and SND [27].

The limitation of the study is that we had no patients with SND and syncope of different than vasovagal origin. Therefore, we are not able to confirm whether group 1 patients really had concurrent vasovagal syncope or they just presented the reflex nature of syncope episodes in SND.

The importance of SACT assessment is still unclear. The Strauss method was the first to estimate SACT and remains the most widely used. It is supposed to be more reliable, but it is time-consuming and has numerous limitations. The method by Narula has an advantage of simplicity but the liabilities are similar to the first method. Based on our previous experience in transoesophageal pacing, we decided to use both methods of SACT assessment to avoid too many missing data.

It has been suggested that the chaotic reaction of the sinus node (SN) to premature impulses is typical for SND. Breithardt *et al.* have interpreted it as a result of SN automatism and sinoatrial conduction disturbances [28]. Sadowski and Szwed reported chaotic behaviour of sinoatrial conduction in 8.6% of patients with SND [29]. They proposed that this chaotic reaction itself indicates SND.

In our study, patients with SND and suspected VVS (group 1) had greater SACT St variability than all other subjects. Additionally, there was no correlation between greater SACT St variability and a positive HUTT result. Thus, increased SACT St variability is the phenomenon characterizing coexistence of SND and VVS. We hypothesize that the main reason for greater SACT variability is the distinct autonomic modulation of a dysfunctional sinus node. Schuessler proposed a new model of the SN based on recent research data [30]. He assumed that the SN consists of cells with different intrinsic rates and that there are specialized pathways

within the node and a limited number of exit sites. Besides, there is a heterogeneous distribution of autonomic receptors. Such a complex structure may cause different disturbances of sinus rhythm, especially when structural and autonomic changes overlap.

However, there are some technical problems concerning the indirect method of SACT assessment, which is critically dependent on regularity of the sinus cycle. Further studies in larger study groups are needed to ascertain that SACT St variability of sinus rhythm is not just an effect of sinus rhythm irregularity.

The basal state variability of SNRT, cSNRT and IIP in group 1 patients was similar to that in group 2 and significantly greater than the corresponding values in groups 3 and 4. This may suggest that increased basal state variability of SNRT, cSNRT and IIP is typical for SND. The only explanation we have for greater variability of the above-mentioned parameters in group 2 is the increased sympathetic modulation of the sinus node before AB. Once more, an additional group composed of patients with syncope caused by SND alone would possibly facilitate the answer.

Clinical, electrographic and electrophysiological features of SND can be triggered by disturbances of the autonomic nervous system [7]. They can be isolated or concomitant to structural damage of the sinus node. Since Jordan *et al.*' study, the terms "functional" and "intrinsic" dysfunction of sinus node have been accepted [31]. Assessment of intrinsic heart rate by pharmacological autonomic blockade has become one of the most widely used tests of sinus node function. In our study, pharmacological autonomic blockade was not only the way to detect an intrinsic dysfunction of the sinus node. The AB revealed many additional electrophysiological features, especially in patients with SND and VVS.

During transoesophageal pacing, among various properties of sinus node assessed at baseline and with the use of AB, there is also a possibility to test the Wenckebach point, which is considered to reflect atrioventricular (AV) nodal conduction [11]. WP refers to the pacing rate (during incremental atrial pacing) at which AV nodal Wenckebach (Mobitz I) block occurs. In patients with SND the presence of concomitant atrioventricular node dysfunction is important because it affects therapeutic decisions (e.g. the type of implanted pacemaker) [7]. In the present study, patients with SND and VVS had lower WP than patients with neither SND nor VVS. In the basal state, abnormal atrioventricular conduction was more frequent in both groups with VVS. However, it seems that patients with concomitant SND might also have decreased atrioventricular node function which persists after

autonomic blockade, indicating organic dysfunction of the AV node. In contrast, subjects with VVS and without SND had mostly functional impairment of AV node conduction, which was due to increased parasympathetic drive.

In conclusion, patients with concurrent sinus node dysfunction and vasovagal syncope have distinct electrophysiological features. This group is characterized by a greater SACT St variability compared to patients without incidents of syncope. Apart from abnormal SNRT, cSNRT and IIP, patients with SND have greater variability of these parameters in the basal state. In patients with SND and concurrent vasovagal syncope the variability of SNRT, cSNRT and IIP decreases after autonomic blockade, indicating increased vagal modulation in the basal state. Transoesophageal atrial pacing is a useful procedure in patients with syncope, especially when the coexistence of more than one cardiac cause is suspected. The protocol after pharmacological autonomic blockade is an essential part of the procedure which can reveal different electrophysiological parameters depending on the distinct aetiology of incidents.

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