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An Abnormal Neural Reflex Plays a Role in Causing Syncope in Sinus Bradycardia

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Objectives. **This study investigates the role of an abnormal neural reflex in causing syncope in patients with sinus bradycardia.**

Background. **Syncope is commonly considered an indication of severity in sinus bradycardia. However, the occurrence of syncope is unpredictable, and the prognosis appears to be similar in patients with and without syncope.**

Methods. **Head-up tilt testing (60° for 60 min), carotid sinus massage in the supine and standing positions, 24-h Holter ambulatory electrocardiographic (ECG) recording and electrophysiologic study before and after pharmacologic autonomic blockade were performed in 25 patients with sinus bradycardia and syncope (group I, sinus rate <50 beats/min, age 71 ± 12 years) and 25 patients with sinus bradycardia and no neurologic symptoms (group II, sinus rate <50 beats/min, age 67 ± 16 years).**

Results. **Clinical characteristics and ambulatory ECG monitoring data were similar in the two study groups. A positive response (induction of syncope or presyncope with hypotension and/or bradycardia) was obtained by head-up tilt testing in 15 group I (60%) and in 3 group II (12%) patients ($p < 0.001$) and by carotid sinus massage in 11 group I (44%) and 6 group II (24%) patients (p = NS). Results of at least one test (head-up tilt testing or carotid sinus massage, or both) were positive in 19 group I (76%) and 9 group II (36%) patients ($p < 0.01$). Basal and intrinsic corrected sinus node recovery time did not differ significantly between the two groups. An abnormal intrinsic heart rate was present in 66% of group I and 26% of group II patients ($p < 0.01$). The different percentage of positive findings on head-up tilt testing and carotid sinus massage in the two groups was independent of the presence of intrinsic sinus node dysfunction.**

Conclusions. **These results indicate that an abnormal neural reflex plays a role in causing syncope in patients with sinus bradycardia. This reflex seems to be unrelated to the severity of sinus node dysfunction, even if the latter could enhance the cardioinhibitory response.**

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Syncope is commonly considered an indication of severity in sinus bradycardia. However, the occurrence of syncope is unpredictable (1–3), and the prognosis appears to be similar in patients with and without syncope (4). A problem still under debate is whether syncope in sinus bradycardia is an expression of exhaustion of intrinsic sinus node function or of abnormal neural reflexes. In the present study we investigated the electrophysiologic properties of the sinus node and the presence of an abnormal neural reflex in two groups of patients with sinus bradycardia—one with syncope and another without neurologic symptoms.

Methods

Patients. We studied 25 consecutive patients with sinus bradycardia and syncope (group I) and 25 consecutive patients with sinus bradycardia and no neurologic symptoms (syncope, presyncope or dizziness) (group II). Diagnosis of sinus bradycardia was made if a sinus rate of <50 beats/min at rest, not induced by drugs, was consistently present on several rest standard electrocardiograms (ECGs) recorded diurnally for 3 to 4 days. The clinical characteristics of the patients are shown in Table 1. In group I, 19 patients had organic heart disease (hypertensive cardiovascular disease in 12, ischemic heart disease in 6, aortic regurgitation in 1). In group II, 15 patients had organic heart disease (hypertensive cardiovascular disease in 8, ischemic heart disease in 7). We included only patients in New York Heart Association functional class I or II because heart failure markedly modifies autonomic tone. No patient engaged in an exercise program. Thyroid function was normal in all patients.

All patients underwent a careful standardized basic investigation, including a complete history and physical and neurologic examination, baseline laboratory testing, orthostatic blood pressure determination, 12-lead ECG, chest roentgenogram, echocardiogram and electroencephalogram. Exercise stress testing was performed only in patients with suspected or diagnosed coronary disease or with organic heart disease. Other investigations, such as Doppler flow

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Table 1. Clinical Features of the Two Groups of Patients With Sinus Bradycardia

	Group I (sinus bradycardia and syncope) (n = 25)	Group II (sinus bradycardia and no neurologic symptoms) (n = 25)	p Value
Age (yr)	71 ± 12	67 ± 16	NS
Men	16	21	NS
Structural heart disease	19	15	NS
Syncopal episodes	2.5 ± 2.3	0	
Trauma	5	0	

meter examination of neck vessels, brain computed axial tomography and coronary angiography, were performed only rarely, when requested by the consultant neurologist or when clinically appropriate. Moreover, all patients underwent electrophysiologic study, head-up tilt testing and carotid sinus massage. All cardioactive and vasoactive drugs were discontinued at least 5 half-lives before the examinations. Informed consent was obtained from all patients.

Electrophysiologic study. Electrophysiologic study was performed after the introduction of two quadripolar catheters—one in the right atrium and the other in the His bundle area. The normal range of intrinsic heart rate was defined according to the Jose and Collison formula (5): 118.1 − (0.57 × age) ± 16. Maximal corrected sinus node recovery time was measured, as previously described (6), during the basal state and after autonomic blockade (propranolol, 0.2 mg/kg body weight, and atropine, 0.04 mg/kg). Corrected sinus node recovery time was measured by atrial pacing at cycle lengths of 600, 500, 430, 370 and 330 ms. Abnormal results were considered to be (5,7) intrinsic heart rate below normal range and maximal corrected sinus node recovery time >500 ms before and >385 ms after autonomic blockade. Atrial and ventricular extrastimulation were performed only in patients with underlying heart disease or with a history of palpitation. Ventricular stimulation was carried out at two right ventricular sites—the apex and outflow tract. The protocol used for the induction of atrial and ventricular arrhythmias included 1 to 3 extrastimuli delivered during sinus rhythm and during multiple drive cycle lengths (600, 500 and 400 ms) and bursts of rapid pacing at progressively increasing rates. Electrophysiologic study was not performed in two patients because of the appearance of atrial fibrillation at the beginning of the investigation (one patient in group I and one in group II) and in another patient in group II because of technical problems. Patients with the following abnormalities suggestive of definite or potential causes of syncope were excluded from the study: typical history of situational syncope (micturition, defecation, cough and swallowing syncope); typical history of vasovagal syncope (syncope induced by unpleasant, frightening, anxiety-filled or painful events or by instrumentation); postural hypotension (orthostatic decrease in systemic blood pressure >30 mm Hg); aortic stenosis; hypertrophic cardiomyopathy; seizure and other neurologic disorders; subclavian steal syndrome; HV interval ≥70 ms; spontaneous or induced sustained (>30 s) and rapid (>180 beats/min) supraventricular arrhythmias; spontaneous unsustained (>10 consecutive beats) ventricular tachycardia; spontaneous or induced sustained ventricular tachycardia, ventricular fibrillation or torsade de pointes.

Carotid sinus massage. Both carotid sinus massage and head-up tilt testing were performed in an isolated room, with patients in a nonfasting state, always in the morning between 8 and 11 AM. Both right and left carotid sinuses were massaged in the supine and erect positions for 10 s during ECG monitoring and closer manual measurements of systolic blood pressure, as previously described (8–10).

Head-up tilt testing. A table with a foot plate support was used. Patients were connected to a standard cardiac monitor for continuous evaluation of heart rate; frequent (every 5 min or more often) blood pressure measurements were performed by cuff sphygmomanometer. The values obtained by this method are not very precise but are adequate to define syncope. Heart rate and blood pressure were monitored during an initial period of supine rest for 10 min and during the subsequent period of head-up tilt testing at 60° for 60 min or until syncope developed. As soon as syncope occurred, the patient was rapidly returned to the supine position. No complications were observed during performance of the tests.

Definitions. Syncope was defined as a transient loss of consciousness with inability to maintain postural tone. Presyncope was defined as the complex of premonitory signs and symptoms of imminent syncope (i.e., severe lightheadedness, severe weakness, transient graying of vision or hearing loss) with difficulty in maintaining postural tone. The response to the induction tests was defined as positive only when syncope or presyncope in association with bradycardia (or asystole) or hypotension, or both, occurred. The cardioinhibitory response during carotid sinus massage was defined as the development of ventricular asystole lasting ≥3 s and during head-up tilt testing as the development of ventricular asystole lasting ≥3 s or heart rate ≤45 beats/min with a >30% decrease in baseline heart rate. The vasodepressor response was defined as a decrease in systolic blood pressure ≤80 mm Hg. These limits were arbitrarily chosen on the basis of published reports and our own experience that symptoms usually occur only when heart rate and blood pressure decrease below these limits.

Statistical analysis. Statistical analysis was performed by the Student *t* test, Fisher exact test or chi-square test, as appropriate.

Results

Electrocardiogram and Holter monitoring. Heart rate at rest, evaluated by standard ECG, was 44 ± 4 beats/min in group I and 46 ± 3 beats/min in group II (p = NS); 24-h

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Table 2. Holter Ambulatory Electrocardiographic Monitoring Data in the Two Groups of Patients

	Group I	Group II
24-h HR (beats/min)		
Mean	51 ± 5	54 ± 6
Minimal	36 ± 6	38 ± 6
Maximal	89 ± 18	90 ± 24
Pauses >2.5 s	8 ± 27	5 ± 7
Patients with pauses >2.5 s	13	11
Longest RR interval (ms)	2,748 ± 2,108	3,002 ± 978
SPBs	288 ± 351	462 ± 753
VPBs	50 ± 155	171 ± 543

There were no significant differences between groups for any of the variables shown. Values presented are mean value ± SD or number of patients. HR = heart rate; SPBs = supraventricular premature beats; VPBs = ventricular premature beats.

Holter recording data did not show significant differences between the two groups (Table 2).

Carotid sinus massage and head-up tilt testing. Positive responses to carotid sinus massage and head-up tilt testing in the two patient groups are listed in Table 3. Carotid sinus massage responses were positive in 11 group I (44%) and 6 group II (24%) patients (p = NS). In all patients the response was cardioinhibitory or mixed. A greater proportion of patients in group I than in group II had a positive response on head-up tilt testing (15 [60%] of 25 vs. 3 [12%] of 25, $p < 0.001$). In the 15 group I patients with a positive result on head-up tilt testing, the response was cardioinhibitory or mixed in 10 (67%) and vasodepressor in 5 (33%). Similarly in the three group II patients with a positive head-up tilt testing result, the response was cardioinhibitory or mixed in two (67%) and vasodepressor in one (33%). The prevalence of cardioinhibitory responses was significantly higher in group I than in group II ($p < 0.05$), whereas the prevalence of vasodepressor responses was only insignificantly higher in group I. Asystole ≥3 s was observed in two patients (one in group I, one in group II). In group I, a positive response occurred after 30 ± 13 min of head-up tilt testing. More precisely, the test result was positive within the 1st 30 min in six patients, between min 31 and min 45 in six patients and between min 46 and min 60 in three patients. In group II, a positive response occurred after 31 ± 19 min of tilt. It was positive within the 1st 30 min in one patient, between min 31 and min 45 in one patient and between min 46 and min 60 in one patient. In group I, all patients with a positive response during head-up tilt testing recognized the induced syncope as identical or similar to the spontaneous syncope. Both carotid sinus massage and head-up tilt testing yielded a positive result in seven group I (28%) and no group II patients. At least one test was positive in 19 group I (76%) and 9 group II patients (36%) ($p < 0.01$).

Table 3. Positive Responses to Carotid Sinus Massage and Head-Up Tilt Testing in the Two Groups of Patients

	Group I (n = 25)	Group II (n = 25)	p Value
Positive CSM response			
Total positive responses	11 (44)	6 (24)	NS
Cardioinhibitory or mixed response	11 (44)	6 (24)	NS
Vasodepressor response	0	0	
Positive HUT response			
Total positive responses	15 (60)	3 (12)	< 0.001
Cardioinhibitory or mixed response	10 (40)	2 (8)	< 0.05
Vasodepressor response	5 (20)	1 (4)	NS
Positive CSM or HUT response	19 (76)	9 (36)	< 0.01

Values are presented as number (%) of patients. CSM = carotid sinus massage; HUT = head-up tilt testing.

Electrophysiologic study. During electrophysiologic study (performed in 24 group I and 23 group II patients), neither the basal nor the intrinsic maximal corrected sinus node recovery time differed significantly between the two groups (966 ± 947 vs. 670 ± 674 ms and 1,958 ± 2,746 vs. 997 ± 1,577 ms, respectively). Intrinsic maximal corrected sinus node recovery time was abnormal in 20 (83%) of 24 group I and 16 (69%) of 23 group II patients (p = NS), whereas an abnormal intrinsic heart rate was more prevalent in group I than in group II (16 [66%] of 24 vs. 6 [26%] of 23, $p < 0.01$). In group I, 5 (33%) of the 15 patients with a positive head-up tilt testing result showed a normal intrinsic heart rate and 10 (67%) an abnormal one. Of the nine patients with a negative head-up tilt testing result, three (33%) showed a normal intrinsic heart rate and six (67%) an abnormal one. In group I, 3 (30%) of the 10 patients with a positive carotid sinus massage result had a normal intrinsic heart rate and 7 (70%) an abnormal one. Of the 14 patients with a negative carotid sinus massage result, 5 (36%) had a normal intrinsic heart rate and 9 (64%) an abnormal one. The difference in percent of positive head-up tilt testing and carotid sinus massage results in the two groups of patients was independent of the presence of intrinsic sinus node dysfunction (Mantel-Haenszel test, p = 0.05) (Fig. 1).

Discussion

Sinus bradycardia is a relatively benign condition because the overall survival rate of patients with an established sinoatrial disorder is similar to that of the normal population (1,2,4,11,12). Moreover, the prognosis does not appear to be different between patients with and without neurologic symptoms (4). The course of symptoms is very variable from patient to patient. Syncope may not reappear for several years in ≈30% to 40% of subjects. Moreover, not uncommonly, the syncope represents an isolated manifestation (1–3). These data are in favor of a reflex origin of syncope, not an impairment of intrinsic sinus node function. In the latter case, in fact, the clinical course should be different.

Brignole et al. (10) recently observed a high prevalence of positive responses to carotid sinus massage and head-up tilt testing in patients with sick sinus syndrome and syncope

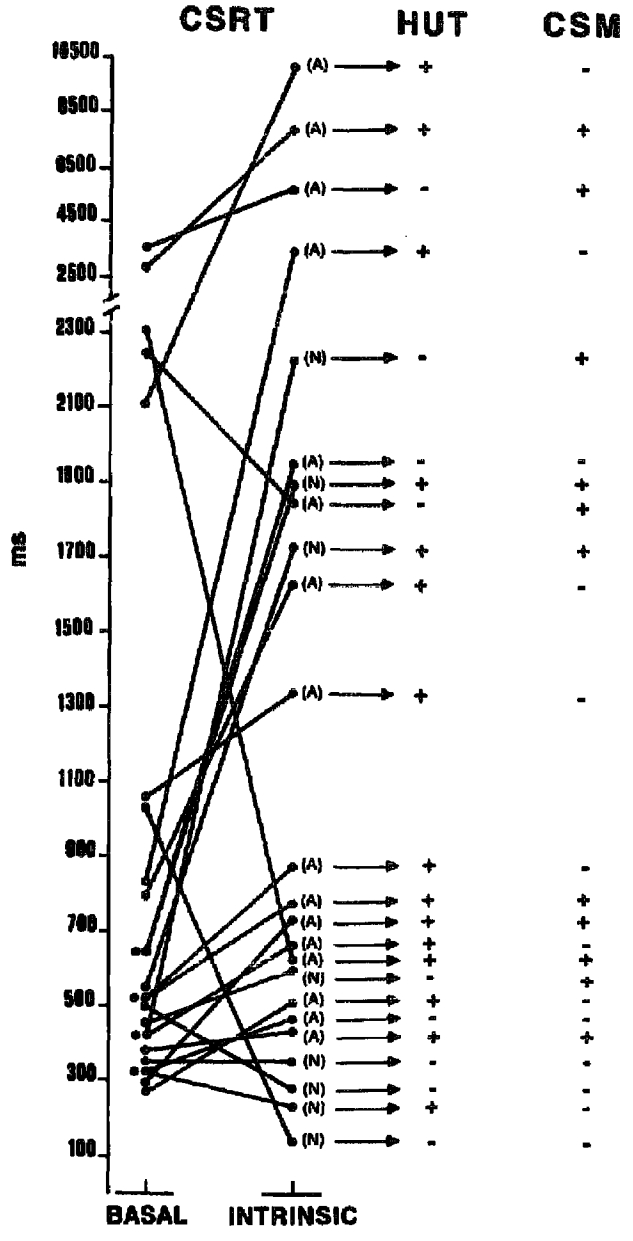

Figure 1. The basal and intrinsic corrected sinus node recovery time (CSRT) and the response to head-up tilt testing (HUT) and carotid sinus massage (CSM) are shown for each patient. Positive responses (+) to the tests occurred in patients with normal or prolonged intrinsic (or basal) corrected sinus node recovery time. (A) = abnormal intrinsic heart rate; (N) = normal intrinsic heart rate; − = negative response.

(60% and 54%, respectively). The prevalence of positive responses to these tests was similar to that observed in patients with normal sinus rate and syncope of uncertain origin. Brignole et al. hypothesized that an abnormal neural reflex plays a major role in causing syncope in patients with sick sinus syndrome. In their study, however, it was not defined whether a sinus node dysfunction can enhance the cardioinhibitory efferent reflex and therefore predispose to the positivity to these tests (i.e., whether in patients with sick sinus syndrome "false positive" responses may occur). For this reason we studied two groups of patients—one with sinus bradycardia and syncope and one with sinus bradycardia but without neurologic symptoms. Clinical characteristics and Holter monitoring data in the two groups of patients were similar. These two groups therefore appear to be comparable. We did not include patients with heart failure or abnormalities suggestive of a definite or potential cause of syncope so as to investigate, as correctly as possible, the role of an abnormal neural reflex.

Among our patients with sinus bradycardia and syncope, a positive response to head-up tilt testing occurred in 60%, an incidence similar to that previously reported in subjects with unexplained syncope (approximately 50%) (9,13–20). In the patients with sinus bradycardia and no neurologic symptoms, this incidence was significantly lower (12%) ($p < 0.001$). Also the incidence of positive responses to carotid sinus massage was higher in patients with syncope than in those without (44% vs. 24%), even if the difference did not reach statistical significance. A positive response to at least one test was observed in a very high proportion of group I patients (76%). In the patients with sinus bradycardia and no neurologic symptoms, positive head-up tilt testing response occurred in 12%, an incidence slightly higher than that previously reported in control subjects without syncope (approximately 7%) (9,10,14,15,17,18,20–22). In the patients with sinus bradycardia and no syncope, a positive carotid sinus massage test occurred in a rather high proportion (24%). During this test the receptors are stimulated directly whereas in head-up tilt testing they are stimulated indirectly. In previous studies, where carotid sinus massage was performed with the method we utilized, a positive response to this test was observed in 3% to 4% of control patients with normal sinus rhythm and no syncope (9,10). Therefore, the results that we obtained in patients with sinus bradycardia and no neurologic symptoms suggest that a sinus node disorder can predispose to cardioinhibitory responses. However, the incidence of a positive response to head-up tilt testing and carotid sinus massage was much higher in the patients with sinus bradycardia and syncope. In patients with sinus node disorder, syncope therefore appears to be mainly related to an abnormal neural reflex. However, we cannot exclude the possibility that in a few patients intrinsic sinus node dysfunction, more prevalent in group I, may induce syncope by itself. It is also possible that the intrinsic sinus node involvement and the abnormal neural reflex are both an expression of the same degenerative pathologic process because the mean age of patients with sinus node dysfunction is high. In 28% of group I patients, responses to both carotid sinus massage and head-up tilt testing were positive, thus raising the possibility that there is a common autonomic nervous system pathway or related etiologies. The association of positive responses to different tests in patients with syncope has been previously reported (9,23,24). We did not perform the isoproterenol test because there are few and very contradictory data with regard to the sensitivity and specificity of this test (9,16,19,21,25,26).

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Conclusions. Our results show that, at least in the majority of cases, a patient with sinus bradycardia is symptomatic for syncope only if he or she is affected with an anomalous neural reflex in addition to the sinus node dysfunction. These results can explain why syncope is unpredictable in patients with sinus bradycardia and why this symptom has no prognostic relevance. These results suggest therapeutic possibilities different from pacemaker implantation in sinus bradycardia, that is, pharmacologic treatment by utilizing drugs effective in the prophylaxis of neurally mediated syncope (14,17,20,27–29).

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