Assessment of Sinus Node Function in Patients with the Sick Sinus Syndrome

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SUMMARY
Thirty-one patients with symptomatic sinus node dysfunction were evaluated with electrocardiograms, Holter monitor recordings, exercise, isoproterenol infusions, atropine administration, Valsalva maneuvers, carotid sinus massage, and overdrive pacing. Four basic clinical subsets were recognized: (1) carotid sinus hypersensitivity (2) bradyarrhythmia-tachycardia syndrome, (3) episodic sinus arrest, and (4) persistent symptomatic sinus bradycardia. The study group demonstrated a normal heart rate response to exercise and isoproterenol infusion (%Δ = +95 exercise, +144 isoproterenol) in the face of diminished responsiveness to atropine administration (%Δ = +23). Marked carotid sinus hypersensitivity was demonstrated in eight patients, and four patients demonstrated slight abnormalities during performance of Valsalva maneuvers. Significant suppression of sinus node dysfunction was observed following atrial overdrive in the study group (postspacing pause = 3087 ± 464 msec) as compared to patients without significant sinus node function (postspacing pause = 1073 ± 63 msec) (P < 0.001). In patients with intact V-A conduction, ventricular overdrive also resulted in sinus node suppression (postspacing pause = 1901 ± 357 msec). There was a marked decrease in the degree of sinus node depression following atropine administration. Ten of 31 patients demonstrated various degrees of A-V block following atrial pacing at rates less than 100 beats/min.

It is concluded that the present methods of evaluation of sinus function, especially sinus node recovery time following overdrive pacing, may prove of value in the investigation of patients with syncope of unknown etiology.

Additional Indexing Words:
Isoproterenol  Atropine  Valsalva maneuver  Carotid sinus massage
Overdrive pacing

RECENT REPORTS have described a spectrum of clinical problems associated with symptomatic sinus bradycardia.1-6 This condition usually manifests itself by syncope related to periods of sinus arrest, marked sinus bradycardia, and/or brady-tachyarrhythmias. Ferrer has called attention to the complexities of the clinical management of this syndrome and suggested the name sick sinus syndrome.7 Little information is available concerning the physiologic abnormalities of sinoatrial node (SAN) function in these patients. This study

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was therefore undertaken in an attempt to more clearly define the underlying physiologic features of this syndrome complex.

Methods

The study group was composed of 31 patients (15 females and 16 males) with a mean age of 69 years, range 31–85 years. The patients’ presenting symptoms were either recent dizzy spells, syncopal episodes, or palpitations. Documentation of the type of arrhythmia was obtained by either standard ECG or continuous 10-hour ECG (Holter monitor) recording. The study procedure is described below.

Carotid Sinus Stimulation. During continuous electrocardiographic and intraarterial pressure monitoring, the effects of massaging first the right and then the left carotid sinus for a period of up to 10 sec were noted.

Valsalva Maneuver. The effects of graded Valsalva maneuver were determined using an occlusive nose clip and a mouthpiece connected to a venous pressure transducer (Statham P23db series). Maneuvers were performed for 10 sec at 10, 20, 30, and 40 mm Hg measured oropharyngeal pressure.

Exercise or Isoproterenol. Patients were then subjected to the stress of: (1) limited exercise using either a bicycle ergometer in the supine position while in the catheterization laboratory, or via treadmill at 10% grade using standard technic; or (2) intravenous isoproterenol administration at rates of 1–2 µg/min.

Pacing Studies. Utilizing standard technics the patients were paced for 30-sec periods at rates of at least 90, 110, 130, and 150 beats/min. Pacing was abruptly stopped at the end of each period to determine the extent of sinoatrial node (SAN) suppression as defined by duration of the postpacing pause. In 14 patients, simultaneous His bundle electrocardiograms were recorded by the technic described by Scherlag et al. 11

Atropine. Following completion of the above procedures, atropine was given intravenously (0.025 mg/kg; 1.1–2.5 mg total dose administered) and the series of studies repeated.

Report of Selected Cases

Previous investigators have commented on the various clinical patterns of sinus node dysfunction. In this study, a variety of clinical situations became apparent as illustrated by the following case reports.

Carotid Sinus Hypersensitivity

Patient L. L. is a 61-year-old male with a history of syncope. Physical examination, neuro-

Figure 1

Carotid sinus hypersensitivity. (A) Twelve-lead electrocardiogram. (B) Record obtained during right carotid massage. The upper trace is a lead II electrocardiogram. The middle trace is the left femoral artery (LFA) pressure with its pressure calibration (0–160 mm Hg) shown to the right of the panel. The lower trace is a marker. Carotid sinus massage was begun at the arrow (CSM) and was abruptly followed by prolonged sinus arrest. The pause was terminated by a sinus beat. A time calibration is shown at the top of the figure.

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logic consultation, electroencephalogram, upper gastrointestinal series, gallbladder series, Holter monitor, and routine laboratory data were all within normal limits. Studies performed demonstrated both marked hypersensitivity to carotid sinus massage (fig. 1) and moderately abnormal SAN recovery time. Following this study, the patient underwent elective transvenous pacemaker implantation and in a subsequent follow-up (after 10 months) has been free of symptoms.

**Bradycardia-Tachycardia Syndrome**

Patient E. S. is an 85-year-old female with a 15-year history of increasing protracted episodes of symptomatic bradycardia and tachycardia. Admission physical examination was normal; however, continuous monitoring demonstrated heart rates as slow as 25 beats/min, alternating with rates as rapid as 150 beats/min. During the transition period between these rhythms, pronounced sinus arrest lasting 3–5 sec was observed without evidence of a subsidiary pacemaker. Subsequently, the patient was studied demonstrating marked bradycardia alternating with supraventricular tachycardia (fig. 2) and moderate SAN suppression following overdrive pacing (postpacing pause = 2600 msec). At the completion of these studies, a permanent ventricular demand pacemaker was implanted, and the patient's arrhythmias have been successfully controlled (11 months) with combined pacing and antiarrhythmic drug therapy.

**Figure 2**

 Bradycardia-tachycardia syndrome. (A) Twelve-lead electrocardiogram. (B) His bundle recording obtained during an episode of marked sinus bradycardia. The upper trace is a lead II electrocardiogram. The lower trace is the His bundle electrogram with the A, H, and V depolarizations labeled. A 1-sec time mark is shown at the top of the figure. Heart rate (HR), AH, and HV conduction times are shown to the right of the figure. (C) His bundle electrograms recorded during an episode of tachycardia with figure legends as in (B). Note the short VA conduction time, long AH time, and retrograde P waves (lead II).
Episodic Sinus Arrest

Patient M. U. is a 31-year-old male with a 2-year history of recurrent syncope. Initial evaluation was normal, including exercise testing, cardiac catheterization with selective coronary arteriography, and the study protocol (see Methods). The patient was restudied 2 months later because of recurrent syncope. A 10-hour Holter tracing at this time demonstrated sinus arrest during a syncopal episode, as shown in figure 3. Subsequently, the patient had a permanent ventricular demand pacemaker implanted and has remained symptom free for 24 months following discharge.

Persistent Symptomatic Sinus Bradycardia

Patient C. B. is a 74-year-old female with a 5-year history of asymptomatic sinus bradycardia (50-60 beats/min). In the 3 months prior to hospital admission, frequent episodes of dizziness and syncope were noted associated with marked sinus slowing (30-40 beats/min) and without chest discomfort or other cardiovascular symptoms. On admission, physical examination was within normal limits except for a pulse rate of 42 beats/min. During continuous monitoring a sinus rate of 25-42 beats/min was noted (fig. 4).

During the study marked sinus bradycardia, profound suppression of the sinoatrial node following overdrive pacing (postpacing pause = 6000 msec), and normal response to atropine administrations and exercise were observed. A permanent transvenous ventricular demand pacemaker was implanted with the patient remaining symptom free (10 months) since discharge.

Results

Carotid Sinus Stimulation

This maneuver, performed in all patients, was associated with moderate slowing of the sinus rate in 23 patients: control heart rate = 50 beats/min, control R-R interval = 1191 ± 64 msec (mean ± SEM); carotid sinus massage heart rate = 36 beats/min, R-R interval = 1687 ± 94 msec; %Δ = -42. Very pronounced depression of sinus rate (sinus arrest

Figure 3

Episodic sinus arrest. (A) Twelve-lead electrocardiogram. (B) Continuous record obtained from a Holter monitor recording (modified V5). A 1-sec time calibration and a 1-mv voltage calibration are shown at the top of the figure. This recording demonstrates a sudden absence of sinus activity without a subsidiary pacemaker. After a pause in excess of 10 sec, there is a sudden return to sinus activity. During the interval the patient had a syncopal episode.
SINUS NODE IN SICK SINUS SYNDROME

Figure 4
Persistent symptomatic sinus bradycardia. (A) Twelve-lead electrocardiogram. Rate is 46 beats/min. (B) Monitor lead rhythm strip demonstrating sinus rhythm at a rate of 35 beats/min. A 1-sec time calibration and a 1-mv voltage calibration are shown to the right of the figure.

of 3000–6000 msec) was noted in the remaining eight patients (fig. 1). In three instances, institution of prolonged atrial pacing was required to restore cardiac rhythm and maintain adequate hemodynamic status. For four of these patients, carotid sinus hypersensitivity was the sole or major manifestation of sinus node dysfunction. In all instances, the response to carotid sinus massage was markedly abbreviated on administration of atropine.

Valsalva Maneuver
This study was performed in 21 patients, and two different responses to the performance of graded Valsalva maneuvers were noted. Seventeen patients demonstrated a normal hemodynamic and chronotropic response as previously reported. However, four patients demonstrated an inappropriate chronotropic response in the face of hemodynamic changes (fig. 5). Despite substantial

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Figure 5

Valsalva maneuvers. The upper trace shows a lead II electrocardiogram; the middle trace shows the left femoral artery (LFA) pressure with a calibration (0–160 mm Hg) to the right of the panel; and the lower trace shows a recording of the oropharyngeal pressure with a calibration (0–20 mm Hg) to the right of the panel. A 1-sec time calibration is shown at the top of the figure. The Valsalva maneuver was begun at the arrow (start of Valsalva) and resulted in prompt drop in systolic pressure. Note the prompt fall in femoral artery pressure unassociated with any significant rate change (82 beats/min control; 80 beats/min Valsalva). With termination of the Valsalva maneuver, there is no pressure overshoot and a modest cardioacceleration (heart rate 93 beats/min).

changes in peripheral blood pressure, none of the patients studied demonstrated a profound increase or decrease in sinus rate during or following the Valsalva maneuver. No substantial differences were observed when the maneuver was performed at varied oropharyngeal pressures.

Exercise or Isoproterenol

The SAN response to supine or treadmill exercise was evaluated in 14 patients, all of whom demonstrated a progressive increase in sinus rate consistent with the degree of exercise (control = 61 beats/min; exercise = 116 beats/min; \( \% \Delta = +88 \)). An additional 12 patients, unable to perform adequate exercise, were tested via isoproterenol infusion and also responded with prompt SAN acceleration (control = 52 beats/min; isoproterenol = 118 beats/min; \( \% \Delta = +127 \)).

Pacing Studies

SAN recovery time in response to overdrive atrial pacing was determined in the entire patient group. In 29 of the 31 patients there was a prolonged suppression of SAN function (mean maximum postpacing pause = 3164 ± 334; normal = 1073 ± 67 msec) (fig. 6A). In eleven patients with intact 1:1 V-A conduction, the effects of ventricular overdrive pacing were compared to atrial overdrive pacing. When paced at similar rates, more severe SAN suppression was noted following atrial overdrive (postpacing pause = 3087 ± 464 msec) than ventricular overdrive (postpacing pause = 1901 ± 357 msec). Ten of 31 patients developed either pronounced first-degree or type I second-degree A-V block when paced at rates less than 100 beats/min. Of these patients, eight had simultaneous His bundle recordings which localized the site of block to the A-V node in all instances. Isoproterenol was infused in four of these patients, resulting in marked abbreviation of A-H time associated with an enhanced ability to conduct at rapid pacing rates.

Atropine Administration

Intravenous atropine was given to all patients to ascertain its effects on basic sinus rate, overdrive suppression, Valsalva maneuver, and carotid sinus massage. All previous abnormal responses were markedly abbreviated and/or returned to normal.

For the entire study group, atropine increased sinus rate from 52 beats/min (P-P interval = 1159 ± 52 msec) to 64 beats/min (P-P interval = 938 ± 45 msec (\( \% \Delta = +23 \)). This is in contrast to the pronounced increase in sinus rate in the 12 patients also challenged
by low-dose isoproterenol infusion (control heart rate = 52 beats/min; after atropine = 64 beats/min; following isoproterenol = 118 beats/min; \%Δ = +23 atropine; \%Δ = +127 isoproterenol). In these 12 patients, the maximum pause following atrial overdrive decreased from 3087 ± 464 msec to 1211 ± 174 msec following atropine (fig. 6B).

**Discussion**

Determination of the etiology of syncopal episodes not infrequently taxes the acumen of the clinician, especially in the case of patients who do not demonstrate evidence of central nervous system or metabolic disease, or overt rhythm disturbance. A systematic approach is needed to evaluate possible cardiac etiologic factors related to syncopal-like symptoms. This study offers such a physiologic approach toward the evaluation of symptomatic patients.

**Carotid Sinus Stimulation**

Eight patients in the present study developed an exaggerated response to carotid sinus massage (asystole exceeding 3 sec). Although increased responsiveness to carotid sinus massage is more common in the elderly, the

![Figure 6](image)

**Figure 6**

Atrial overdrive suppression. (A) The upper trace is a lead II electrocardiogram; the middle trace is the atrial electrogram (AEG); and the lower trace is the femoral artery pressure (LFA) with a pressure calibration of (0–160 mm Hg) at the right of the panel. Cessation of atrial pacing (130 beats/min) is followed by pronounced suppression of the sinus pacemaker. The pause is terminated by a sinus beat. (B) Similar to (A), but the record is obtained 5 min after atropine administration. Note that cessation of pacing is followed by a very abbreviated sinus pause and then return to sinus rhythm.
profound sinus arrests observed in this small segment of our study group is well beyond the anticipated results for patients in this age group. Nevertheless, in only one case was a hypersensitive carotid sinus the sole abnormality discovered and, apparently, the etiologic factor in the patient's symptoms.

Valsalva Maneuver

In all patients studied by this technic, the expected pressure responses were observed; yet, bunted rate responses were occasionally observed. Performance of graded Valsalva maneuvers did not, however, help to delineate further the patient population, nor did it aid in diagnostic evaluation of problem patients.

Atropine Administration

Relative atropine unresponsiveness (rate increase of +25%; normal up to 64% increase) was a characteristic feature of our patient population (27 of 31 patients). This unresponsiveness may be due to: (1) diminished resting vagal influence, although the results with isoproterenol suggest enhanced vagal tone is less prominent than decreased sympathetic tone; (2) too low a dose of atropine that may in fact induce a paradoxical bradycardia, but this has not been observed using doses of atropine comparable to those in the present study or (3) occult S-A node-atrial conduction abnormality obscuring the increase in SAN rate. However, several patients did demonstrate a prompt and marked positive chronotropic response to atropine. Prior studies in patients with somewhat similar clinical features have also documented limited positive chronotropic responses following oral or intravenous atropine administration in similar dosage ranges.

Exercise and Isoproterenol

Because of the advanced age of many of the patients, detailed evaluation of sinus node response to exercise or beta-stimulation was not carried out in all patients. In those patients so studied, the response was within the expected normal range suggesting that diminished responsiveness to endogenous or exogenous catecholamines is not a significant factor. However, a diminished level of resting sympathetic tone may be present.

Overdrive

The most common abnormality seen was the abnormal response to overdrive atrial pacing. Studies with overdrive pacing demonstrate suppression of SAN automaticity. Previously defined limits of SAN suppression were substantially exceeded following overdrive pacing in our present patient group (postpacing pause = 3164 ± 334 msec, abnormal; 1073 ± 67 msec, normal; P < 0.001). The abnormal response may be explained by: (1) excessive release of acetylcholine or hyperresponsiveness to acetylcholine; (2) excessive extracellular K+ or increase in K+ flux; or (3) diminished sympathetic activity in the face of normal or increased parasympathetic responsiveness. However, all abnormal responses could be markedly reduced following administration of atropine. Three of 31 patients did not demonstrate significantly abnormal SAN recovery following overdrive, which may be the result of partial SAN entrance block during artificial pacing. Similarly, the disparity seen between atrial vs ventricular overdrive suppression may be related to incomplete SAN penetration during retrograde atrial activation.

The present investigation has demonstrated apparent normal sympathetic reactivity and abnormal parasympathetic reactivity in the patients with sick sinus syndrome. The response to Valsalva, overdrive, atropine administration, and carotid sinus massage suggests that hyperresponsiveness to acetylcholine may be more important than increase in resting vagal tone. Overdrive pacing has proved to be the most valuable method of evaluating patients with potential S-A node disease, and it is recommended that this technic be used in the evaluation of patients suspected of having abnormalities of S-A node function.

This report emphasizes the difficulties encountered in establishing an appropriate physiologic diagnosis. Documentation of the type of rhythm disturbance responsible for symptoms may not always be readily obtainable, and repeated use of continuous 10-hour
ECG (Holter) monitoring may prove invaluable.

The therapy for disorders of sinus node function has not been clarified. In spite of evidence suggesting relative unresponsiveness to vagolytic agents, the use of permanent pacemaker implantation has not always been utilized.6 However, pacing is of value in the management of the patient with the bradycardia-tachycardia syndrome and allows the initiation of a successful antiarrhythmic program or may, in fact, entirely eliminate the need for antiarrhythmic drugs.

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