Disease of the Sinoatrial Node Associated with Bradycardia, Asystole, Syncope, and Paroxysmal Atrial Fibrillation

By R. I. Birchfield, M.D., E. E. Menefee, M.D., and G. D. N. Bryant, M.D.

Disease of the sinoatrial node due to coronary arteriosclerosis is rare. An unusual combination of arrhythmias attributed to disease of the sinus node and the effects of various pharmacologic agents, especially atropine, are described and discussed.

Sinus bradycardia has been associated with a number of entities, both normal and pathologic; however, it is usually of a transient nature. It has been found in 30 per cent of healthy young males,\(^1\) the well-trained athlete,\(^2\) and has been associated with pregnancy, particularly the post partum period.\(^3\) Its incidence markedly exceeds what might be expected in starvation, myxedema, jaundice, increased intracranial pressure, beriberi, labyrinthitis, convalescence from certain infectious diseases, and bilateral thoracic sympathectomy.\(^4-6\) In a series of 6,786 medical hospital admissions Kirk and Kuorning\(^4\) found sinus bradycardia in 515 patients, or 7.6 per cent; syncope due to the sinus bradycardia occurred in only 1 patient. Sinus bradycardia due to arteriosclerotic heart disease is rare.

As can be seen from examination of the above list of entities, there are diverse causes of sinus bradycardia. These causes may be classified as neurogenic or non-neurogenic. By blocking of vagal activity with atropine increased vagal activity has been demonstrated in young men,\(^7\) starvation,\(^4\) and increased intracranial pressure.\(^8\) Short\(^9\) describes 4 patients with alternating sinus bradycardia associated with a variety of tachycardias. Sinus standstill was present in 2 patients and a wandering pacemaker in 3 patients. Atropine, effort, or emotion was found to accelerate the rate considerably, usually to a normal sinus rhythm, in all these patients.

Asystole with normal sinus rhythm and nodal rhythm have been described respectively by Laslett\(^10\) and Wedd and Wilson.\(^11\) These periods of asystole and concomitant syncope were ascribed to increased vagal tone and were abolished by atropine.

Non-neurogenic causes would include changes in the sinoatrial (S-A) node brought about by either the direct action of bacterial toxins, metabolic defects, or ischemic changes secondary to vascular disease. Winternitz and Selye\(^12\) have reported a case of sinus bradycardia due to thrombosis of the artery to the sinus node.

Persistent sinus bradycardia that does not respond to exercise, emotion, or atropine is rare. Brasil\(^13\) reported an organic sino-atrial depression, which did not respond to any of the above stimuli, in 13.5 per cent of 200 cases of Chagas' disease, and attributed this depression to a toxin from Trypanosoma cruzi that acted specifically on the sinoatrial node. The heart rate in these patients ranged between 50 and 70.

Pearson\(^14, 15\) also reported a case of sinus bradycardia associated with asystole and syncope that failed to respond to exercise, atropine, and numerous pharmacologic stimuli.

In clinical practice, all the above bradycardias associated with asystole must be differentiated from the Adams-Stokes attacks, which occur in patients with any degree of atrioventricular block and in about 60 per cent of the patients with complete heart block; it should be kept in mind also that not all syncopal episodes associated with this entity are due to asystole, but to rapid ventricular arrhythmias as well.\(^16, 17\)

The patient to be presented below has the outstanding features of the combination of sinus bradycardia, asystole with syncope, a
sinoatrial node unresponsive to atropine or other stimuli, and transient atrial fibrillation. Atropine had an interesting action on the atrioventricular (A-V node) but no demonstrable effect on the S-A node. We propose that organic disease of the S-A node probably secondary to coronary arteriosclerosis is the major factor in this case and, though vagal activity may be important in some of the attendant arrhythmias, it is not the cause of the persistent sinus bradycardia.

In publishing this case we repeat the remark of William Stokes, made 110 years ago, that "the observations are published with the view of drawing the attention of the Profession to a combination of cerebral and cardiac phenomena, of which our knowledge is still imperfect."18

CASE REPORT

The patient, a 70-year-old white widow, entered the hospital on January 13, 1956, with the chief complaint of diplopia of 3 weeks' duration. There also was a history of bradycardia for 10 years and intermittent syncopal attacks for 5 years, with a recent increase in their frequency.

The diplopia first was noticed on waking, several days prior to Christmas, 1955; there were no other accompanying symptoms except for a slightly unsteady gait. Both symptoms disappeared whenever she looked to the left or covered either eye.

Ophthalmologic and neurologic examinations, including visual fields and skull x-rays, were normal. It was the neurologist’s opinion that the diplopia was due to a right lateral rectus palsy secondary to thrombosis of a branch of the basilar artery.

Ten years ago a slow pulse rate of 40 was noted. Known hypertension had been present for the past 5 to 6 years, with blood pressures ranging between 200/120 to 245/140. Syncopal episodes began 5 years ago and occurred at 3- to 4-month periods until 18 months ago, when they became more frequent.

Twelve months ago she was hospitalized because of dyspnea and ankle edema; there was no chest pain. Following a prolonged period of bed rest and a regimen of diuretics and low-salt diet she improved, but since then had received diuretics intermittently because of recurrent ankle edema. She had not been digitalized.

Over the past year the syncopal attacks appeared on the wane, but 3 months ago increased in frequency with as many as 24 in a day. She had never fallen with these episodes, as there was a preceding aura of the sensation of blood rushing to her head and she either would sit or lie down quickly. Occasionally the periods of syncope would be preceded by a burst of rapid palpitations, then the heart would seem to stop and syncope would ensue. There was a tendency for the attacks to occur more frequently while the patient was lying down, rather than when sitting or moving about. The usual period of unconsciousness did not exceed 1 to 2 minutes by her estimation; often she awoke with a feeling of nausea, but within a few minutes was able to resume her work. A generalized nocturnal seizure occurred 3 years ago accompanied by urinary incontinence and a 20-minute period of unresponsiveness.

Significant in the past history were 2 separate episodes of thrombophlebitis with bilateral involvement of the legs.

On physical examination she appeared to be a pleasant, alert, cooperative, somewhat anxious, moderately obese woman. The positive findings included a paresis of the right lateral rectus muscle. Fundoscopic examination showed moderate arteriolar narrowing with minimal arteriovenous nicking, but no hemorrhages or exudates. Both carotid arteries were firm but pulsatile. The lungs were clear to auscultation and percussion. The left border of cardiac dullness extended almost to the left anterior axillary line, the cardiac rhythm appeared at times regular, at 32 per minute, but there were other periods of marked irregularity with occasional pauses up to 3 seconds in duration. The pulmonic second sound was increased and louder than the aortic and there was a diffuse, harsh, low-pitched, grade III systolic murmur, best heard over the aortic area that radiated toward the neck. The blood pressure was 180/80. Tender 2+ pitting pretibial edema was present almost to the knees. Neurologic examination, except for the right sixth cranial nerve palsy, was within normal limits.

The hemogram was normal, and urinalysis showed specific gravities of 1.010 to 1.018 on random samples and no abnormalities. The corrected sedimentation rate was 9 mm. per hour. Blood chemistry evaluations, including nonprotein nitrogen, cholesterol, and electrolytes, were within normal limits. The basal metabolic rate ranged from minus 19 to minus 7 per cent, the 24-hour radioiodine uptake was 10 per cent, and the protein-bound iodine was 5.2 µg per cent. Chest x-ray showed that the heart was slightly enlarged to the left and the right hilum was prominent from what was thought to be a vascular shadow. The admission electrocardiogram showed a rate of 24 per minute, P-R 0.18 second, and QRS 0.06 second; it was interpreted as showing a marked sinoatrial bradycardia but otherwise to be within normal limits (fig. 1).

Mercuhydrin was given shortly after admission and a 1200-calorie, 35-Gm. fat, 400-mg. sodium diet was instituted along with bed or chair rest. The weight dropped from 81.75 Kg. to 77.95 Kg. in the first 24 hours, and the ankle edema disappeared in 2 to 3 days.
The patient continued to have syncopal attacks, which were heralded by a moan, facial pallor, and closing of the eyes. During the shorter periods of asystole she could hear but felt unable to move, and during the longer periods (9 seconds) minimal convulsive movements of the right arm were noted. The onset of syncopal symptoms occurred between 4.4 and 4.8 seconds after asystole (fig. 2).

On the fifth hospital day the electrocardiogram showed a sinus bradycardia with a rate of 26; however, the P-R interval varied between 0.18 and 0.12 second. Occasionally the P-R interval was at its shortest just before a period of asystole. Resumption of the heart beat after a period of asystole was invariably by a nodal beat followed by other irregular nodal beats and gradual return to a sinus bradycardia. Atropine, 1.2 mg. intravenously, was given after these observations. Ninety seconds after injection a nodal rhythm began with retrograde P waves at 32 beats per minute (fig. 3). After the atropine there were no syncopal attacks for 6 hours and numerous electrocardiograms taken during this time continued to show an A-V nodal rhythm with retrograde P waves. The only side effects were dryness of the mouth and mild blurring of vision; she expressed a preference for these symptoms to the syncopal attacks.

Seven hours after atropine sinus bradycardia again was present. After sitting up 8 times a slightly irregular nodal rhythm with intermittent retrograde P waves appeared, which reverted after 45 seconds to a sinus bradycardia at 28 per minute. Carotid sinus pressure was applied without any demonstrable effect. Methantheline bromide, 50 mg. orally, failed to abort the attacks that night and produced no changes in rhythm.

On the sixth hospital day, several periods of asystole were recorded and 100 mg. of methantheline bromide orally was followed in 35 minutes by an irregular rhythm with mixed sinus and nodal beats. Asystole was not prevented, however, and 3 hours after methantheline bromide a sinus rhythm at 21 per minute was present. Exercise at this time produced a rate of 30 per minute, with P-R intervals varying between 0.18 and 0.10 second, and an occasional nodal beat; in the sitting position there was a change to a nodal rhythm with retrograde P waves at 29 beats per minute, and in the supine position there was a short burst of nodal bigeminy followed by a sinus beat, then asystole of 4.9 seconds accompanied by syncope.

The attacks of syncope continued during the evening and in the early morning of the seventh hospital day she noticed the onset of rapid palpitations. An electrocardiogram showed atrial fibrillation with a ventricular rate of 110 per minute and an isoelectric or inverted T wave in lead II (fig. 4). Ten hours after the onset of palpitations they terminated

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**Fig. 1.** Control electrocardiogram, sinus bradycardia at 26 per minute.

**Fig. 2.** Asystole of 6 seconds' duration resulting in syncope. Note recovery by a nodal beat.

**Fig. 3.** Conversion to a low nodal rhythm at 32 per minute, 90 seconds after atropine, 1.2 mg. intravenously.

**Fig. 4.** Paroxysmal atrial fibrillation at 110 per minute.

**Fig. 5.** Mid-nodal rhythm at 40 per minute after atropine, 2.0 mg. intravenously.
suddenly and spontaneously, and were followed immediately by a period of syncope.

A midafternoon electrocardiogram showed a nodal rhythm at 24 per minute. Atropine, 2.0 mg. intravenously, increased the rate to 40 and the nodal rhythm without retrograde P waves persisted (fig. 5). Four hours later there was a nodal rhythm with retrograde P waves. Ephedrine, 15 mg. intramuscularly, was given whereupon nodal bigeminy mixed with a sinus bradycardia began 1 to 2 minutes later.

Twelve minutes later nodal tachycardia at 100 per minute was present, which was followed in sequence by a short burst of paroxysmal atrial tachycardia with varying degree of atrioventricular block, a 9-second period of asystole, and a nodal rhythm at 45 per minute. During the tachycardia there was inversion of the T wave in lead II.

On the eighth hospital day sinus bradycardia at 27 per minute again was present. Isopropyl norepinephrine, 10 mg. sublingually, was followed in 12 minutes by a nodal rhythm with retrograde P waves at 34 per minute; however, syncopal attacks continued.

Since atropine had provided the most symptomatic relief, it was given 1.5 mg. orally every 8 hours on the ninth hospital day. The syncopal attacks then occurred only in the few hours preceding each dose of atropine; the patient was given 1.5 mg. every 6 hours with considerable reduction in the number of attacks. She was discharged on the next day.

The patient continued to have syncopal attacks, but only in the sixth hour after atropine, so it was given every 5 hours.

She was seen on a clinic visit on April 4, 1956, and had had no further attacks after changing to the 5-hour schedule. She had gradually lengthened the interval between doses to 8 hours and still had not had another syncopal attack. The diplopia had cleared and she had resumed her normal activities, but was slightly bothered with a dry mouth, visual blurring, and constipation.

Physically she appeared much improved and had lost weight, from 81 to 68 Kg., the blood pressure was 160/90, and the heart was regular at 34 per minute. An electrocardiogram showed a wandering pacemaker with impulses arising from the S-A node and the A-V node with both high and low A-V nodal beats.

She remained symptom free until October 1956, when the syncopal attacks recurred 10 to 12 days after being started on reserpine and mecamylamine. These drugs were stopped on October 18 but the attacks continued over the next 4 days, requiring hospitalization. Over the next 5 to 6 days the attacks decreased and stopped on the sixth day. She was maintained on atropine 1.2 mg. every 5 hours, and when seen in the clinic in December 1956 had remained symptom free.

**Discussion**

In this patient the S-A node had been so altered that neither vagal nor sympathetic impulses had any effect on its rate. Atropine increased the irritability of the A-V node and allowed it to control the rate of the heart.

The vagus nerves have equally numerous endings in both the S-A and A-V nodes. The heart rate is influenced by both the vagal and sympathetic nerves. The vagal influence is usually negated by giving atropine, 2 mg. parenterally; the usual response is an increase in heart rate of 37 to 42 beats per minute.

Vagal control over the heart also is lessened by exercise.

The accelerating influence of the sympathetic nerves to the heart is shown by bilateral thoracic sympathectomy. Such patients have a resting bradycardia and acceleration of the heart rate is both delayed and lessened in response to exercise. When patients with bilateral thoracic sympathectomy including the stellate and celiac ganglia are given atropine, the resultant resting heart rate is below that which is expected in normal persons.

The failure of the sinus rate to increase in our patient after atropine points strongly to disease of the S-A node as the basis of the persistent bradycardia, rather than abnormal vagal activity. The nature of the disease involving the S-A node is unknown. The authors believe that there is sufficient clinical substrate to place coronary arteriosclerosis high on the list of suspected diseases.

Upon review of the literature, the mechanism of production of sinus bradycardia and accompanying periods of asystole is uncertain. Pearson has described a case very similar to ours and in his first article postulated that atheromatous embarrassment of the blood supply to the S-A node was the cause, but autopsy several years later failed to disclose any anatomic lesions, either gross or microscopic, of either sinus or the A-V nodes or any evidence of coronary arteriosclerosis. A bronchogenic carcinoma was found that involved the mediastinal structures but not the heart. Pearson did not believe that the tumor could impose a constant vagal stimulus without vagal escape.
Intermittent vagal stimulation by the tumor might account for the periods of asystole, but the failure of atropine to relieve the bradycardia or the periods of asystole cannot be explained by invoking vagal stimulation as the causative mechanism.

Pearson also reviewed the literature on similar arrhythmias, but could not find any conclusive evidence concerning their possible etiology.

Winternitz and Selye describe a case of sinus bradycardia of sudden onset; at autopsy infiltration of lymphocytes, polymorphonuclear neutrophils, and plasma cells in the area of the sinus node and thrombosis of the artery to the S-A node were found. The patient’s critical condition and early death apparently made clinical study of this bradycardia inopportune.

The periods of asystole related to the S-A node have at least 2 probable causes: either sinus arrest or sinoatrial block. Clinically, sinus arrest is associated with vagal reflexes such as can be induced by gagging or a hypersensitive carotid sinus. The usual measures used to induce vagal reflexes were without effect in our patient.

Sinoatrial block was reviewed briefly by Kisch and Zucker in 1942 without definite agreement as to whether it is due to functional causes or pathologic lesions. They presented a case of sinoatrial block and retrograde atrial conduction associated with permanent complete heart block, and at autopsy there was moderate sclerosis of the coronary arteries, a scar in the upper portion of the intraventricular septum, and atrophy of the muscular tissue in the region of the A-V node. Friedberg states that sinoatrial block usually is associated with digitalis or quinidine administration, or organic lesions involving the sinus node.

Electrocardiographically, sinoatrial block usually shows a prolonged P-P interval that approximates a multiple of the normal P-P interval; this phenomenon does not appear to be present in our case, but the moderate arrhythmia associated with the bradycardia and the fact that the beat was always resumed from an A-V nodal impulse makes this difficult to ascertain.

Experimental sinoatrial block with A-V nodal escape has been produced by Scherf. In order to obtain rhythms with bradycardia or long periods of standstill he found it necessary to damage the sinus node and depress the A-V node as well. Complete severance of the vagi had no influence on these experiments.

A more definitive analysis of this type of rhythm will have to wait until either chance or ingenious technical development allows the use of fine exploring electrodes, such as used by Puech and co-workers or Lanari, Lambertini, and Revin on the human heart.

The chief therapeutic benefit derived from atropine in this case was the development of an A-V nodal rhythm. Wilson produced A-V nodal rhythms with atropine; vagal stimulation after 1 mg. hypodermically slowed the S-A node and allowed the A-V node to serve as the pacemaker. This action of atropine depends on its abolishing vagal influences at the A-V node before affecting the sinus node; however, there is some evidence that atropine may affect the A-V node per se, independent of the release of vagal influence. Our patient fortunately was relieved by the development of an A-V nodal rhythm; Pearson’s case developed A-V nodal extrasystoles after atropine, but was not freed of syncopal attacks due to asystole.

The use of other drugs, including methantheline bromide, isopropyl norepinephrine, and ephedrine will not be discussed here; Haymond and Bellet, and Nathanson and Miller adequately described the actions of these drugs that might be expected to be of benefit.

It appeared that vagal activity was of importance in the production of syncope, since the A-V node still responded to vagal activity. Increasing vagal activity by lying down increased the frequency of the attacks, while decreasing vagal activity by standing or by atropine lessened the frequency of the syncopal attacks. Exercise also lessens vagal tone and in this patient produced a nodal rhythm. These vagal effects seemed not to operate at all through changes in the S-A node activity, but did determine how quickly the A-V node assumed control of impulse formation once sinus standstill had occurred.

Experimentally, atrial fibrillation is more
readily produced by acetylcholine after cooling the S-A node. The episode of paroxysmal atrial fibrillation in our case draws an interesting but speculative parallel.

The duration of the syncopal attacks following the use of reserpine is compatible with its known period of activity. The relative parasympathetic predominance produced by reserpine accentuates the importance of autonomic activity in the production of asystole.

Due to the periodicity of the asystole, no claims can be made that atropine will continue to be as beneficial as apparently it now is. The necessary changes in the dosage schedule of the atropine serve to emphasize the waxing and waning influences that produce the asystole. The use of atropine appears well worth a trial in cases similar to this one.

**SUMMARY**

The clinical picture produced by disease of the sinoatrial node is described and illustrated by a case report. Disease of the S-A node has been implicated as the cause of the persistent bradycardia. Autonomic influences over the A-V node have been implicated in the production of asystole. In this patient any maneuver decreasing vagal tone was of benefit because these circumstances allowed the rhythm of the heart to be controlled by the A-V node. Sitting up, exercise, and atropine were all effective means of initiating nodal rhythm.

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**Sommierno in Interlingua**

Le tableau clinic de morbo del nodo sinoatrial es descritib e illustrate per le reporto de un caso. Morbo del nodo sino-atrial ha essite implicate comu causa del persistente bradycardia. Influencias autonome super le nodo atrio-ventricular ha essite implicate in le production de asystole. In le presente patience omne manovra capace a reducer le tono vagal esseva benefic, proque sub iste conditiones le nodo atrio-ventricular poteva regular le rhythmio cardiae. Seder se erecte, exercitio, e atropina, omne istes esseva medios efficace pro initiare un rhythmio nodal.

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Medical Eponyms

By Robert W. Buck, M.D.

Corrigan Pulse. Aortic regurgitation had been described by several physicians before the appearance of a communication by Dominic John Corrigan (1802-1880), Physician to the Charitable Infirmary of Dublin and Lecturer on the Theory and Practice of Medicine at St. Patrick’s College, Maynooth, in the Edinburgh Medical and Surgical Journal 37: 225-245 (April 1), 1832, “On Permanent Patency of the Mouth of the Aorta, or Inadequacy of the Aortic Valves,” but his account has become a classic.

“When a patient affected by the disease is stripped, the arterial trunks of the head, neck, and superior extremities immediately catch the eye by their singular pulsation. At each diastole the subclavian, carotid, temporal, brachial, and in some cases even the palmar arteries, are suddenly thrown from their bed, bounding up under the skin. . . . Though a moment before unmarked, they are at each pulsation thrown out on the surface in the strongest relief.”
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