The sick sinus syndrome

A study of 15 cases

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Fifteen patients with features of sick sinus syndrome are reported. Their manifestations varied from severe sinus bradycardia, sinoatrial block, and arrest, to paroxysmal supraventricular tachyarrhythmias, reflecting the underlying unstable sinoatrial node. The rhythm can be bradycardic, tachycardic, or mixed. Thyrotoxicosis tops the list of aetiological factors, others being ischaemic heart disease, drug-induced, subarachnoid haemorrhage, cardiomyopathies, and myocarditis. Syncope, usually due to prolonged sinoatrial arrest, was the presenting feature in half of the cases, and some 70 per cent of patients showed radiological evidence of cardiomegaly, though clinical cardiac failure was uncommon. Therapeutic responses to vagolytic and sympathomimetic agents were variable, particularly discouraging in patients with mixed bradycardia and tachycardia. Cardiac pacing may be life-saving in some cases.

Disorders of the sinoatrial node manifest themselves in various forms. They range from sinus bradycardia, multifocal atrial ectopics, runs of atrial tachycardia, to prolonged sinoatrial arrest with temporary total cardiac standstill. The hallmark of their expressions is an unstable sinoatrial node with its capricious rhythms till they reach their established stage when they often lapse into chronic atrial fibrillation. Such manifestations of the 'sick sinus node', or the 'sick sinus syndrome', as defined by Lown (1967), is characterized by 'chaotic atrial activity with continual changes in P wave contour with bradycardia interspersed with multiple and recurring ectopic beats with runs of atrial or nodal tachycardia'. We have set out to review our experience of 15 patients who showed clinical and electrocardiographic features of sick sinus syndrome.

Subjects and methods

Over a one-year period, from October 1969 to October 1970, all patients seen at the Department of Medicine of the General Hospital, Singapore, particularly those attending the Cardiac Clinic, were screened, and their electrocardiograms scrutinized for manifestations of sick sinus syndrome. Patients with acute myocardial infarction monitored in the Coronary Care Unit were excluded, as sick sinus syndrome, when present in this group, was mostly a transient phenomenon. One of us (L.G.S.) also screened the Endocrine (Thyroid)

Clinic for unstable sinoatrial rhythms before established atrial fibrillation among 100 newly diagnosed thyrotoxic patients.

The diagnosis of thyrotoxicosis was based on clinical grounds, protein-bound iodine levels, and radio-iodine uptake studies, while the diagnosis of ischaemic heart disease was mainly made on clinical and electrocardiographic assessments.

Patients diagnosed as having sick sinus syndrome were followed up regularly at weekly to monthly intervals, and serial electrocardiograms taken as occasions arose. Patients with bradycardic rhythms were assessed for their responses to exercise, intravenous atropine, sympathomimetic agents, and if necessary cardiac pacing.

The electrocardiograms were analysed, and manifestations of sick sinus syndrome were classified into the following groups based on Ferrer's classification.

Group I: persistent and severe sinus bradycardia.

Group II: episodes of isolated sinoatrial block¹.

Group III: sinoatrial suppression with (a) escape rhythm, as in case of *transient* sinoatrial arrest; (b) replacement rhythm, as occurring with *chronic* suppression of the sinus node, resulting in replacement of sinus rhythm with an escape mechanism, e.g. chronic nodal bradycardia; and (c) rescue rhythm due to delayed emergence of the secondary pacemaker resulting in *prolonged* sinoatrial arrest – such 'rescues' often take the form of short bursts of paroxysmal tachyarrhythmias.

¹ *Note:* Electrocardiographically, sinoatrial block is distinguished from sinoatrial arrest in that the latter is a consecutive series of the former.

Group IV: isolated atrial fibrillation (unaccompanied by other arrhythmias) as a manifestation of sick sinus syndrome.

Case reports

The following case summaries may serve to illustrate the protean manifestations of sick sinus syndrome.

Case 1 (thyrotoxic cardiomyopathy with sick sinus syndrome) (Patient No. 3)¹ A 21-year-old Chinese girl was admitted in March 1969 with symptoms of thyrotoxicosis for 2 years, confirmed by radio-¹³¹I study and a large goitre. Her pulse rate varied between 60 and 120 a minute with a blood pressure of 150/60 mmHg. Her heart was clinically enlarged with a soft systolic murmur over the left sternal edge, but there was no evidence of cardiac failure. A chest film taken 2½ years before was said to be normal. Her electrocardiograms in March revealed sinoatrial arrest with an unstable atrial pacemaker and paroxysmal atrial flutter. She was started on carbimazole therapy in April, and as she became euthyroid, she lapsed into severe chronic sinus bradycardia and

sinoatrial arrest, with occasional nodal escape beats, the heart rate being about 40 a minute. She developed occasional syncopal spells and became very lethargic; she was pale and her extremities cold from a low output state due to bradycardia. Intravenous atropine accelerated both the atrial and nodal beats, but resulted in atrioventricular dissociation (see Fig. 1B), and this effect lasted only for 20 minutes. Atrial pacing via an Elecath Semifloating Electrode inserted by the bedside under intracardiac electrocardiographic monitor into the right atrium was established at 2 volts at 80 a minute, only for 5 minutes, thereafter, it resulted in a Wenckebach type of response (Fig. 1C), due to abnormality of conduction in the atrial myocardium or the AV node. It was then thought appropriate to float the catheter electrode into the right ventricle, and ventricular pacing was instituted at 2 volts at 80 a minute (Fig. 1D). During pacing her colour improved and extremities became warm, and blood pressure rose from 120/60 to 140/90 mmHg. When she was weaned off the pacemaker 48 hours later, she returned to sinus bradycardia, but with sinus rhythm (Fig. 1E). Forty-eight hours of pacing did not achieve any shrinking in the size of the heart on the chest film (Fig. 2).

¹ Patient numbers are listed in Table 1.

FIG. 1 *Thyrotoxic cardiomyopathy with sick sinus syndrome treated by ventricular pacing.*

FIG. 2 Chest film of patient with thyrotoxic cardiomyopathy, showing gross cardiomegaly with tip of Elecath semifloating electrode in position for ventricular pacing.

Case 2 (thyrotoxic periodic paralysis with unstable atrial pacemaker) (Patient No. 4) A 26-year-old Chinese man was admitted with the complaints of sudden weakness of the legs, and was found to suffer from thyrotoxicosis with periodic paralysis (serum potassium, 2.1 mEq/l.). He was put on carbimazole therapy, and two weeks later he was observed to have an irregular pulse. Electrocardiogram (Fig. 3) revealed evidence of an 'alternating bradycardia and tachycardia' syndrome (Short, 1954), with an unstable atrial pacemaker wandering into the coronary sinus node. The runs of inverted P waves showed varying PR intervals. This recurred in episodes lasting from minutes to hours for a week, then reverted to sinus rhythm as the patient became clinically euthyroid.

Case 3 (thyrotoxicosis and bradycardia-tachycardia-asystole syndrome) (Cheng, 1968; Adelman and Wigle, 1969) (Patient No. 6) A 63-year-old

woman had symptoms of thyrotoxicosis (untreated) for 9 months when she was admitted for syncopal spells from prolonged sinoatrial arrest recurring frequently over one week. In fact, monitoring electrocardiograms revealed cyclical rhythms of the following sequence: paroxysmal atrial tachycardia or fibrillation, terminating abruptly in asystole from prolonged sinoatrial arrest, rescued by bradycardia from a lazy sinus node which slowly warmed up only to be succeeded by atrial fibrillation again (Fig. 4A). Subsequently she was given intravenous atropine for sinoatrial arrest, but with no effect. Soon after she developed three episodes of Adams-Stokes attacks from cardiac standstill. It was then realized that cardiac pacing was the only solution therapeutically. Accordingly, an Elecath Unipolar Semifloating Electrode catheter was inserted via the right basilic vein and manipulated into the right atrium under intra-atrial electrocardiographic monitoring, and atrial pacing was instituted at 70 beats a minute on fixed pacing (Fig. 4B). With stable atrial pacing for 48 hours, she remained perfectly well, the catheter was taken out on the third day due to phlebitis, and she remained in stable sinus rhythm thereafter, while her thyrotoxicosis gradually came under control with carbimazole therapy.

Case 4 (phenothiazine-induced sick sinus syndrome) (Patient No. 9) A 41-year-old man was admitted as a known case of schizophrenia with the history of having taken about a hundred tablets of thioridazine hydrochloride (Melleril) (50 mg each tablet) on the day of admission. He was conscious with a pulse rate of 78 a minute, regular, blood pressure 130/70 mmHg. Heart and lungs were clear, there was no neurological deficit, but the patient refused to talk. Three and a half hours after admission, he suddenly collapsed. Electrocardiogram then revealed paroxysmal atrial fibrillation amidst runs of multifocal atrial ectopics, and sinoatrial arrest. It showed features of 'chaotic atrial mechanism' (Phillips, Spano, and Burch, 1969) characterized by (1) absence of a dominant atrial pacemaker; (2) P waves of at least three morphologies in a single lead; and (3) varying PP, PR, and RR intervals (Fig. 5). He was resuscitated but remained in shock and was treated with isoprenaline drip later. He died 12 hours after admission. There was no documentation of the cardiac rhythm terminally. At necropsy,

FIG. 3 Patient with thyrotoxic periodic paralysis and sick sinus syndrome

his heart did not reveal any macroscopical or microscopical pathology.

Case 5 ('cardiomyopathy' with sick sinus syndrome) (Patient No. 13) A 22-year-old man with complaints of mild exertional dyspnoea was noted since 1964 to have pulsus bigeminus with a faint systolic murmur over the left sternal edge without evidence of cardiac failure. Radiologically, the heart was slightly on the large side with unremarkable configuration. Electrocardiogram (Fig. 6) revealed intermittent sinoatrial arrest, with nodal escape rhythm coupled by retrogradely activated sinoatrial beats. This resulted in clinical pulsus bigeminus. He was thought to have a form of cardiomyopathy of unknown origin. He had remained in such rhythm since 1964. It is interesting to note here that while the sinoatrial node itself has completely lost its own rhythmicity, it is capable of being retrogradely activated to initiate normally conducted sinus beats. Physical exercise and intravenous atropine, sustained-released isoprenaline (Saventrin), did not accelerate the heart significantly. Atrial pacing with a semifloating electrode failed repeatedly to capture the atrium, using stimuli up to 5 volts. Intra-atrial electrocardiograms confirmed the previously described electrocardiographic features. Finally, he was put on tablet orciprenaline (Alupent) 20-40 mg 6-hourly and his heart rate was maintained at about 60-70 a minute, and palpitation became less distressing.

Results

There were 15 patients in this series comprising 6 men and 9 women. The slightly higher female ratio is probably due to the higher proportion of patients with thyrotoxicosis.

Age distribution The age distribution of the 15 patients is shown in Fig. 7. As expected, the peak incidence falls on the 61-70 years age group, mainly because of the high incidence of ischaemic heart disease at this age group.

Thyrotoxicosis, on the other hand, has two peaks of incidence generally, i.e. at the teenage group and about middle age, when they may be complicated by ischaemic heart disease.

The other miscellaneous causes of sick sinus syndrome affect patients of all ages.

Aetiology Table 1 tabulates the aetiology and related clinical features in these 15 cases of sick sinus syndrome.

From this Table, it can be seen that ischaemic heart disease and thyrotoxicosis form the underlying causes of the sick sinus syndrome in 50 per cent of cases in this series. This may have to do with the somewhat selective nature of our collection of cases. In three instances where ischaemic heart disease might have co-existed with thyrotoxicosis, it was likely that

FIG. 4 Patient with thyrotoxicosis and bradycardia-tachycardia-asystole syndrome: 72 hours of atrial pacing restored sinus rhythm.

the former was responsible for the sinoatrial disturbances in view of the fact that such disturbances subsided with antithyroid therapy.

Drug-induced sinoatrial rhythm disturbances were noted in two patients. The striking features among these are, (a) both cases manifested as chaotic atrial mechanism, and (b) they carried a high mortality in that both patients perished.

The rest, the miscellaneous group, had aetiologies varying from subarachnoid haemorrhage to myocarditis and cardiomyopathy, while in 2 patients, the underlying causes were unidentifiable.

Clinical features It is noteworthy that while the sick sinus syndrome due to ischaemic heart disease tended to be bradycardic

FIG. 5 Thioridazine-induced chaotic atrial mechanism, with sinoatrial arrests and paroxysmal atrial flutter in between.

those with thyrotoxicosis tended to be tachycardic, whether paroxysmal or sustained.

Some 50 per cent of patients presented with syncopal spells. Such syncope often stemmed from prolonged sinoatrial arrest, or severe nodal bradycardia. Only on one occasion was it ascribed to paroxysmal atrial tachycardia.

About 70 per cent of patients (10 out of 15) had radiological evidence of cardiomegaly, usually mild. However, clinical cardiac failure was exceptional.

The electrocardiographic features of sick sinus syndrome are analysed and tabulated in Table 2. Though the number of patients in each group is small, there are certain characteristics in each group which are summarized in the Table as 'group characteristics'.

Mortality Of 15 patients, 3 died. Both patients with sick sinus syndrome from drug intoxication perished, while another with subarachnoid haemorrhage died more from the underlying disease rather than sick sinus syndrome itself. Of those who survived, the follow-up period varied between three months and six years.

Response to therapy Table 3 shows the varied responses to drug treatments and pacing.

Only 7 patients with bradycardic rhythm had therapeutic trial to assess various cardiac accelerating agents. The presence of mixed rhythms of bradycardia and tachyarrhythmia frequently made it difficult therapeutically, as very often drug treatment of arrhythmia will potentiate the other. It was in the background of such therapeutic dilemma that our patient (Case 3) was put on fixed atrial pacing with overdriving.

Discussion

Diseases of the sinoatrial node assume a wide spectrum of arrhythmia and conduction defects. The term sick sinus syndrome was first coined by Lown (1967) to denote the group of unstable and chaotic supraventricular rhythm after cardioversion for chronic atrial fibrillation in patients on digitalis, while Ferrer (1968) has reviewed extensively the pathophysiological mechanisms and clinical manifestations of sick sinus syndrome. When such a syndrome is essentially bradycardic, it has been referred to as 'lazy sinus rhythm' (Shaw and Eraut, 1970) (see Case 1). Persistent sinus bradycardia is often the early sign of sinoatrial node disease. It may be so severe as to require permanent atrial pacing (Clarke, Evans, and Milstein, 1970). Such bradycardia

FIG. 6 Patient with pulsus bigeminus from essentially a chronic nodal bradycardiac rhythm for six years.

should not be confused with the well-known physiological bradycardia of the athletes.

Physiologically, the sinoatrial node has the highest rate of impulse formation, which makes it the dominant pacemaker in the normal healthy heart. However, under certain circumstances, diseases of the sinoatrial node, whether organic, as in inflammation or infarction, or functional from autonomic imbalance, may lead to transient or prolonged failure of the spontaneous rhythmicity.

When *transient*, sinoatrial node suppression results in sinoatrial block. The possible mechanisms of this include: (a) A disturbance of impulse formation; (b) abnormal conduction of impulses between the sinus node and the atrial muscle – the so-called ‘exit block’; and (c) atrial unresponsiveness due to sub-threshold impulse formation in the sinoatrial node (Sherf, 1969).

The autonomic system may play a permissive if not an essential role in these.

When *prolonged*, sinoatrial node suppression gives rise to sinoatrial arrest, of a few beats duration, after which cardiac activity may resume with an escape mechanism which may be atrial, nodal, or even ventricular.

Occasionally, spontaneous sinoatrial activity may be continuously or even permanently suppressed, while cardiac function is sustained by an ectopic atrial or junctional rhythm which virtually replaces the sinus rhythm. Patients 13, 14, and 15 with chronic nodal bradycardia probably belong to this group of sick sinus syndrome.

Sometimes, sinoatrial arrest may continue for more than a few beats, due to delayed emergence of an escape pacemaker which, having been delayed, makes a dire-dash ‘escape’ to the rescue, the so-called ‘rescue rhythm’. Such sinoatrial arrests often result in Adams-Stokes attacks and the rescue rhythms often take to bouts of ventricular or supraventricular tachyarrhythmias.

Atrial fibrillation could be a manifestation of disorders of the sinoatrial node too. Thus, chronic atrial fibrillation with slow ventricular rate unassociated with drug therapy (e.g. bi-nodal disease) is often the established stage of sick sinus syndrome, while transient or paroxysmal atrial flutter or fibrillation, whether accompanied by other forms of arrhythmia, could be the early stage of this syndrome. In fact, it is interesting to note that sick sinus syndrome was first coined for the chaotic supraventricular arrhythmia after cardioversion in patients with atrial fibrillation maintained on digitalis. Here the sick sinus node

FIG. 7 Chart showing age distribution of 15 cases of sick sinus syndrome.

TABLE 1 Summary of aetiology and clinical features of 15 cases of sick sinus syndrome

Aetiology	Patient No. (Case No.)	Sex, age (yr)	Pulse rate	Syncope (cause)	Cardiomegaly	Principal rhythm	Sick sinus syndrome group	Survival to date
Ischaemic heart disease	1	M/61	30-60	o	+	Sinus bradycardia + SA block	II	Alive (8 mth)
	2	F/70	40	o	+	Sinus bradycardia	I	Alive (12 mth)
Thyrotoxicosis	3 (Case 1)	F/21	30-50	+ (SA arrest)	+++	Nodal bradycardia + SA arrest	IIIb	Alive (8 mth)
	4 (Case 2)	M/20	110-150	o	-	Wandering pacemaker	IIIa	Alive (3 mth)
	5	F/64	90-200	o	-	Paroxysmal atrial fibrillation	IV	Alive (7 mth)
Thyrotoxicosis + mild ischaemic heart disease	6 (Case 3)	F/63	Unstable	+ (SA arrest)	+	Mixed bradycardia + tachycardia	IIIc	Alive (11 mth)
	7	F/66	Unstable	o	-	Paroxysmal atrial fibrillation	IV	Alive (12 mth)
	8	F/66	Unstable	o	+	Wandering pacemaker + paroxysmal atrial fibrillation	IIIb	Alive (4mth)
Drugs: thioridazine hydrochloride	9 (Case 4)	M/41	Unstable	+ (SA arrest)	-	Wandering pacemaker + paroxysmal atrial tachycardia + SA arrest	IIIb	Dead
Drugs: digoxin	10	M/83	Unstable	o	+	Wandering pacemaker + paroxysmal atrial fibrillation + paroxysmal atrial tachycardia	IIIb	Dead
Cerebral vascular accidents	11	M/85	100	-	+	Wandering pacemaker	IIIb	Dead
Viral	12	F/64	80	+ (? paroxysmal atrial tachycardia)	+	Paroxysmal atrial fibrillation	IV	Alive (6 mth)
? Myocarditis cardiomyopathy	13 (Case 5)	M/22	40-50	+ (SA arrest)	+	Nodal bradycardia	IIIb	Alive (6 yr)
Unknown	14	F/52	30-40	+ (bradycardia)	-	Nodal bradycardia + wandering pacemaker	IIIb	Alive (22 mth)
	15	F/41	30	o	+	Nodal bradycardia + SA arrest	IIIb	Alive (5 mth)

SA, sinoatrial.

TABLE 2 Electrocardiographic group characteristics of sick sinus syndrome

Group	Patient No. (Case No.)	SA block	SA arrest	Escape mechanisms			Atrial fibrill.	Atrial tachycardia	Group characteristics
				Atrial	Nodal	Ventricular			
I	2	-	-	-	-	-	-	-	Essentially bradycardic, with or without SA block; paroxysmal supraventricular tachyarrhythmia conspicuously absent
II	1	+	-	-	-	-	-	-	
IIIa	4 (Case 2)	-	+	+	+	-	-	-	Rhythm can be bradycardic or tachycardic or mixed; SA arrest or chronic suppression, a common feature, with or without SA block; escape mechanisms may be atrial, nodal, or ventricular; supraventricular tachycardia often present: this can (a) recur; (b) lead to SA arrest from post-drive suppression; (c) follow SA arrest as a rescue rhythm
IIIb	3 (Case 1)	+	+	+	+	+	-	-	
	8	+	SA Suppression	-	+	-	+	-	
	9 (Case 4)	+	+	+	+	-	+	+	
	10	+	SA Suppression	-	+	-	+	-	
	11	+	SA Suppression	-	+	+	-	+	
IIIc	13 (Case 5)	+	+	-	+	+	-	-	
	14	+	SA Suppression	-	+	-	-	-	
	15	-	SA Suppression	-	+	-	-	-	
IV	6 (Case 3)	+	+	+	+	-	+	+	Essentially atrial fibrillation, chronic paroxysmal, and unaccompanied by other arrhythmias
	5	-	-	-	-	-	+	-	
	7	-	-	+	+	+	+	-	
	12	-	-	-	-	-	+	-	

TABLE 3 *Response of bradycardic rhythm to therapy*

Sick sinus syndrome group	Patient No.	Aetiology of sick sinus syndrome	Atropine I.V.	Iso-prenaline	Orci-prenaline	Cardiac pacing	Post-pacing
I	2	Ischaemic heart disease	+	o	o	o	
II	1	Ischaemic heart disease	±	o	o	o	
III	3	Thyrotoxic cardiomyopathy	AV dissociation		±	Ventricular	Sinus bradycardia
III	13	? Cardiomyopathy	+	+	+	Unsuccessful	
III	14	Unknown	—	—	+	o	
III	15	Unknown	—	o	o	o	
III	6	Thyrotoxicosis + mild ischaemic heart disease	—	o	o	Atrial	Sinus rhythm

o = Therapeutic agent not tried; — = therapeutic agent tried but no response; ± = therapeutic agent yielded doubtful or marginal response; + = therapeutic agent yielded good response.

may take time to 'warm up' before assuming dominance after cardioversion.

The rhythm in sick sinus syndrome may be classified as follows. (i) Bradycardic, as in Groups I and II; (ii) tachycardic, as in Group IV mostly; and (iii) mixed rhythms, mainly in Group III.

Reviewing the published work one finds that long before the sick sinus syndrome was coined, various forms of allied disorders of similar nature were described. Thus, Short (1954) first described the syndrome of alternating bradycardia and tachycardia where sinus bradycardia was complicated by paroxysmal tachyarrhythmia. Of 4 patients he described, 3 suffered from aortic or mitral valvular diseases. One such syndrome was seen in our series in a patient with thyrotoxicosis with periodic paralysis (Case 2). In this connexion, it is interesting that while all Short's patients failed to respond to routine therapy with digitalis, procainamide, and intravenous atropine, one of them was rendered free from the arrhythmia for 18 months after total thyroidectomy. This syndrome described by Short later comes to bear the name of brady-tachycardia syndrome in recent reports.

Allied to the above-mentioned syndrome is the bradycardia-tachycardia-asystole syndrome first described by Adelman and Wigle (1969) in which the cardiac rhythm occurs in cyclical sequence as given in the order of the syndrome. It is believed (Zipes and Wallace, 1969) that in this syndrome, bradycardia due to the depressed sinus node predisposes to the emergence of ectopic tachyarrhythmia, which in turn, through the mechanism of 'post-drive suppression' from membrane hyperdepolarization (Lange, 1965), further suppresses, in its wake, the already depressed intrinsic rhythmicity of the sinus node, leading

to sinoatrial arrest. The duration of such overdrive suppression of the sinoatrial node has been found to be directly proportional, within limits, to the rate and period of the overdriving tachycardia. Our patient (Case 3) with untreated thyrotoxicosis is an example of this fascinating arrhythmia.

In 1957, Dewhurst described 'malignant auricular arrhythmias' in 4 patients with paroxysms of separate kinds of atrial arrhythmias following one another closely. They were noted for their unstable rhythms, obstinacy to conventional therapeutic agents (e.g. digitalis, quinidine, etc.), progressive cardiac failure, and grim prognosis.

Not only are the rhythms of sick sinus syndrome unstable but they may be chaotic. In fact, 'chaotic atrial mechanisms' (Phillips *et al.*, 1969) have been described in patients with (a) absence of dominant pacemaker, (b) P waves of at least three morphologies in a single lead, and (c) varying PP, PR, and RR intervals. Chaotic atrial mechanisms may be intermittent or sustained, and are often associated with atrial fibrillation. In Burch's series, 3 per cent of patients with chaotic atrial mechanisms were thyrotoxic and 58 per cent of patients were receiving digitalis; it carried a poor prognosis with a hospital mortality of 52 per cent. For comparison, it is noteworthy that 2 out of 3 such patients in our series were associated with drug toxicity — thioridazine hydrochloride and digitalis, while the third was found in a thyrotoxic patient (Patient No. 8). Both the former died while the latter survived.

Similar to chaotic atrial mechanisms is 'multifocal atrial tachycardia' described by Shine, Kastor, and Yurchak (1968). In view of the characteristic resemblances to 'chaotic atrial mechanisms', it has been recently

labelled as chaotic atrial tachycardia (Lipson and Naimi, 1970).

Aetiology of sick sinus syndrome There is a host of aetiological factors in the causation of the sick sinus syndrome.

The artery to the sinoatrial node, like any other artery in the coronary system, can be involved by arteriosclerosis. Circulatory insufficiency and injury to the sinoatrial node can result in transient manifestations of sick sinus syndrome, including sinoatrial block and arrest (Rossi, 1969), and damage to the sinoatrial node in acute myocardial infarction is not an uncommon cause of transient atrial fibrillation and other atrial arrhythmias.

The significant incidence of atrial arrhythmias in thyrotoxicosis and the frequency with which they disappear when thyroid hyperfunction is controlled suggest that thyroxine influences atrial automaticity and excitability, either directly or indirectly. When thyroid hormone is administered to embryonic heart before nerve elements appear, it causes an accelerated rate and sometimes an irregular heart (Markowitz and Yater, 1932). When given to dogs with denervated hearts, it causes tachycardia (Martius and Hess, 1951). This indicates that thyroid hormone has a chronotropic effect directly on myocardium. It is also believed that thyroid hormone accelerates the heart and potentiates emergence of the ectopic pacemaker by sensitizing beta-receptors of the heart to circulating catecholamines (Brewster *et al.*, 1956). Norepinephrine most closely simulates the physiological effects of hyperthyroidism. It is on this basis that beta-blockers have been advocated for the symptomatic treatment of patients with thyrotoxicosis (Howit and Rolands, 1966; McLean, 1967). However, it may be difficult to account for the existence of severe bradycardiac rhythms (such as lazy sinus rhythm) in the thyrotoxic patient. None the less, whatever the unstable supraventricular rhythm, these patients tend ultimately to end up in established atrial fibrillation.

Apart from abnormalities in ST and T waves to simulate patterns of myocardial infarction (Byer, Ashman, and Toth, 1947; Cropp and Manning, 1960), subarachnoid haemorrhage may also induce arrhythmias, particularly of the supraventricular variety. Thus, Hunt, McRae, and Zapf (1969) reported 6 cases of sinus bradycardia and 2 instances of wandering pacemakers in 20 patients with primary subarachnoid haemorrhage. The possible mechanisms producing sick sinus syndrome in subarachnoid haemorrhage probably involve the autonomic sys-

tem. In our series, the patient with subarachnoid haemorrhage (Patient No. 11) developed an unstable sinoatrial rhythm with runs of wandering pacemakers.

Drugs It is well established that digitalis could induce a host of cardiac arrhythmias, and the depressant effect on the sinoatrial node (and other pacemakers) could well be responsible for various manifestations of sick sinus syndrome. In fact, sick sinus syndrome was first described in digitalized patients subjected to cardioversion for chronic atrial fibrillation.

As for thioridazine hydrochloride, it has been well documented that many psychiatric drugs, particularly members of the phenothiazine group, in susceptible individuals, could induce wide ranges of atrial or ventricular arrhythmias (Burda, 1968; Kelly, Fay, and Laverty, 1963).

Myocarditis and cardiomyopathy In these broad categories of heart disease, whether the pathological process is inflammatory, infiltrative, or degenerative, the sinoatrial node may be involved, and in the earlier stages, as in an irritative phenomenon, paroxysmal and transient episodes of arrhythmias could result. Sometimes, neurovegetative changes in the ganglionic plexus supplying the sinoatrial node (Rossi, 1969) associated with the diseases may play a role in the genesis of sick sinus syndrome as well. Thus both chagasic cardiomyopathy (Brasil, 1955) and diphtheritic myocarditis have been found to show sinoatrial node ganglionic plexus degeneration – causing the so-called ‘automatic sinoatrial block’.

Whatever the underlying diseases, it may be said that sick sinus syndrome results either from direct structural damage to the sinoatrial node whether ischaemic in origin or otherwise; or from sympathetic-parasympathetic imbalance as a result of (i) disturbances from circulating hormones or drug agents, or (ii) neurovegetative derangement of the ganglionic fibres to the sinoatrial node by the disease process.

Management The management of patients with sick sinus syndrome has been a challenging and difficult problem. Treatment with vagolytic drugs for the bradycardic rhythm whether sinus bradycardia, nodal rhythm, or sinoatrial block or arrest, stems from the belief that these may be due to vagotonic effect. Generally, responses to atropine, sympathomimetic agents such as isoprenaline (including sustained-release isoprenaline)

and orciprenaline, are discouraging. Only 3 out of our 7 patients with bradycardic rhythm had a favourable response to any one of these drugs. Digitalization for supraventricular tachyarrhythmia in sick sinus syndrome does not seem practical in patients with mixed bradycardia and tachycardia as observed by Short (1954).

The main difficulties involved in therapy of sick sinus syndrome stem from a number of factors.

- 1) The rhythm is often unpredictable, coming on in paroxysms.
- 2) The rhythms are often mixed, with bradycardia intermingled with tachycardia.
- 3) The underlying aetiology in some cases is not identifiable or not remediable, e.g. arteriosclerotic ischaemic heart disease; or even if remediable, as in thyrotoxicosis, it may take time, so that arrhythmia will have to be dealt with in the mean time.
- 4) The management of intermittent but prolonged sinoatrial arrest is even more difficult. Apart from attempting to treat the underlying cause, atrial pacing may help. In cases with alternating bradycardia and tachycardia, or bradycardia-tachycardia-asystole syndrome, atrial pacing at a high rate may be the answer (Rokseth, Gedde-Dahl, and Foss, 1970); it takes care of the severe bradycardia and temporary asystole, while it suppresses the tachycardia by overdriving with fixed rate pacing, or, failing that, it still allows for the safe administration of antiarrhythmic agents without having to worry about aggravating the bradycardic rhythm. This was life-saving in Patient No. 3 (Case 1). However, the high frequency of atrial and atrioventricular disturbances in these patients often compels one to resort to fixed or demand pacing from the right ventricle.

Conclusions

It appears from this series that the sick sinus syndrome may be caused by varied aetiological factors, with thyrotoxicosis heading the list. Untreated, the toxic state hastens the progression of this arrhythmia to atrial fibrillation. Control of toxicity generally cures the syndrome though not invariably so (Case 1). Therapy is difficult in view of the diverse manifestations within the same patient from sinoatrial arrest and bradycardia arrhythmia to atrial tachycardia and chaotic atrial rhythm. In view of the unpredictability of response to the sympathomimetic and vagolytic drugs, cardiac pacing is more reliable in both the bradycardic and paroxysmal tachycardic

group. The mortality of the syndrome is dependent on both the predominant arrhythmic pattern and the underlying condition. The high mortality in the drug-induced group is probably due as much to brain damage and metabolic disturbance as to the arrhythmia itself.

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References

- Adelman, A. G., and Wigle, E. D. (1969). The bradycardia, tachycardia, asystole syndrome. *Canadian Medical Association Journal*, **100**, 75.
- Brasil, A. (1955). Autonomical sino-atrial block; a new disturbance of the heart mechanism. *Arquivos Brasileiros de Cardiologia*, **8**, 159.
- Brewster, W. R., Isaacs, J. P., Osgood, P. F., and King, T. L. (1956). The haemodynamic and metabolic interrelationships in the activity of epinephrine, nor-epinephrine and the thyroid hormones. *Circulation*, **13**, 1.
- Burda, C. D. (1968). Electrocardiographic abnormalities induced by thioridazine (Mellaril). *American Heart Journal*, **76**, 153.
- Byer, E., Ashman, R., and Toth, L. A. (1947). Electrocardiograms with large upright T waves and long QT intervals. *American Heart Journal*, **33**, 796.
- Cheng, T. O. (1968). Transvenous ventricular pacing in the treatment of paroxysmal atrial tachyarrhythmias alternating with sinus bradycardia and standstill. *American Journal of Cardiology*, **22**, 874.
- Clarke, M., Evans, D. W., and Milstein, B. B. (1970). Sinus bradycardia treated by long term atrial pacing. *British Heart Journal*, **32**, 458.
- Cropp, G. J., and Manning, G. W. (1960). Electrocardiographic changes simulating myocardial ischemia and infarction associated with spontaneous intracranial haemorrhage. *Circulation*, **22**, 25.
- Dewhurst, W. (1957). Malignant auricular arrhythmia. *British Heart Journal*, **19**, 387.
- Ferrer, M. I. (1968). The sick sinus syndrome in atrial disease. *Journal of the American Medical Association*, **206**, 645.
- Howit, G., and Rowlands, D. J. (1966). Beta-sympathetic blockade in hyperthyroidism. *Lancet*, **i**, 628.
- Hunt, D., McRae, C., and Zapf, P. (1969). Electrocardiographic and serum enzyme changes in subarachnoid haemorrhage. *American Heart Journal*, **77**, 479.
- Kelly, H. G., Fay, J. E., and Lavery, S. G. (1963). Thioridazine hydrochloride (Mellaril): its effects on the electrocardiogram and a report of two fatalities with electrocardiographic abnormalities. *Canadian Medical Association Journal*, **89**, 546.
- Lange, G. (1965). Action of driving stimuli from intrinsic and extrinsic sources on in situ cardiac pacemaker tissues. *Circulation Research*, **17**, 449.
- Lipson, M. J., and Naimi, S. (1970). Multifocal atrial tachycardia (chaotic atrial tachycardia). *Circulation*, **42**, 397.
- Lown, B. (1967). Electrical reversion of cardiac arrhythmias. *British Heart Journal*, **29**, 469.
- McLean, A. G. (1967). Adrenergic beta-blockade in thyrotoxic crisis. *Medical Journal of Australia*, **2**, 229.

- Markowitz, C., and Yater, W. M. (1932). Response of explanted cardiac muscle to thyroxin. *American Journal of Physiology*, **100**, 162.
- Martius, C., and Hess, B. (1951). The mode of action of thyroxin. *Archives of Biochemistry and Biophysics*, **33**, 486.
- Phillips, J., Spano, J., and Burch, G. (1969). Chaotic atrial mechanism (C.A.M.). *American Heart Journal*, **78**, 171.
- Rokseth, R., Gedde-Dahl, D., and Foss, P. O. (1970). Pacemaker therapy in sino-atrial block complicated by paroxysmal tachycardia. *British Heart Journal*, **32**, 93.
- Rossi, L. (1969). Disturbances in impulse conduction – sino-atrial arrest, sino-atrial block and atrial standstill. In *Histopathologic Features of Cardiac Arrhythmias*. Casa Editrice Ambrosiana, Milan.
- Shaw D. B., and Eraut, D. C. (1970). Sinus bradycardia, sino-atrial block and lazy sinus syndrome. In *Proceedings of the British Cardiac Society*. *British Heart Journal*, **32**, 557.
- Sherf, D. (1969). Editorial. The mechanism of sino-atrial block. *American Journal of Cardiology*, **23**, 769.
- Shine, K. I., Kastor, J. A., and Yurchak, P. M. (1968). Multifocal atrial tachycardia; clinical and electrocardiographic features in 32 patients. *New England Journal of Medicine*, **279**, 344.
- Short, D. S. (1954). The syndrome of alternating bradycardia and tachycardia. *British Heart Journal*, **16**, 208.
- Zipes, D. P., and Wallace, A. G. (1969). Artificial atrial and ventricular pacing in the treatment of arrhythmias. *Annals of Internal Medicine*, **70**, 885.

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