Familial sinoatrial node dysfunction *Increased vagal tone a possible aetiology*

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Clinical and electrophysiological studies of a 13-year-old boy with sinus bradycardia revealed sinus node dysfunction. Long-term follow-up data of members of his family indicated familial sinus node dysfunction. Increased vagal tone was present in all patients. It is suggested that excessive vagal discharge for a prolonged time may be the basic mechanism of sinus node dysfunction in these patients.

Dysfunction of the sinoatrial node is being increasingly recognized in clinical practice. A variety of clinical states have been associated with the underlying pathology of the primary human pacemaker and grouped together as the sick sinus node syndrome (Ferrer, 1968). Sinoatrial node dysfunction appears not only in adults in whom there is a wide aetiological spectrum, but also in children with congenital disorders (James, 1967). This communication describes the clinical and electrophysiological features of a 13-year-old asymptomatic boy with sinoatrial node dysfunction without QT interval prolongation, congenital deafness, or any other congenital anomalies. Long-term follow-up data of members of his family indicative of familial sinoatrial node dysfunction are also presented.

Case reports

Case 1

A boy of 13 years 3 months was referred to the Johns Hopkins Hospital for assessment of his heart condition. The patient had been totally asymptomatic. At 3 years of age routine physical examination showed a slow irregular pulse. Since the age of 3 he was seen every year. There was no history of rheumatic fever or diphtheria. He had not received any medicines. The patient's family had a strong history of bradycardia (Fig. 1). The abnormal physical findings were limited to the cardiovascular system. The pulse rate was 40/min and irregular. Blood pressure was 135/75 mmHg (18.0/10.0 kPa). A

2-3/6 systolic ejection murmur was maximally heard at the lower left sternal border and a 1/6 mid-diastolic murmur at the apex. Chest radiograph showed a cardiothoracic ratio of 0.44 and moderately prominent pulmonary vasculature. Resting surface electrocardiogram (Fig. 2) showed sinus bradycardia at a rate of 35/min and a pattern compatible with left ventricular hypertrophy. Routine blood and urine tests were within normal limits.

Exercise increased the sinoatrial rate to 42/min; 1 mg atropine intravenously increased both the sinus and junctional rate to 50/min, with the sinus impulses capturing the ventricles resulting in a

FIG. 1 The family tree of Case 1 (identified by the arrow). The affected females and males of this family are shown as shaded circles and squares respectively.

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FIG. 2 Resting 12 lead electrocardiogram of Case 1; precordial leads were recorded on half standardization.

bigeminal pattern with a varying degree of aberrant conduction (Fig. 3).

Cardiac catheterization was performed in the post-absorptive state; the pressure measurements were within normal limits and no gradients were found: both the cardiogreen dye curves and oximetry showed no shunt. After the intracardiac pressures were recorded a No. 6 tripolar catheter was advanced through the femoral vein across the tricuspid valve in order to record His bundle electrogram using the standard technique (Scherlag *et al.*, 1969). Another No. 6 quadripolar catheter was inserted through the right median cubital vein and advanced to the superior vena cava-right atrial junction. Two poles of this catheter were used to record a high right atrial electrogram and the other two poles were used to pace the atria. All the intracardiac electrograms, a lead II surface electrocardiogram, and time marks of 10 and 100 ms were displayed on a multichannel switched beam oscilloscope and recorded on photographic paper at a speed of 200 mm/s. The His bundle electrogram showed only a His deflection occurring before each QRS complex. Intermittently beats originating in the sinus node captured the ventricles and these

beats had an AH interval of 140 ms and HV interval of 36 ms. The atria were then paced at various cycle lengths and the pacing was abruptly stopped in order to assess the automaticity of the junctional tissue and the sinus node (Mandel *et al.*, 1971; Narula, Samet, and Javier, 1972). Pacing at a cycle length of 600 ms (100/min), the first escape occurred from the junction at an interval of 1360 ms, whereas the sinus node escaped only at 3200 ms. The atria were then paced at the same cycle length after administration of 1 mg atropine intravenously. Both the junctional and sinus escape interval shortened to 778 ms and 1500 ms, respectively. After administration of atropine the frequency of both the junctional pacemaker and the sinus node increased, with the latter capturing the ventricles alternatively, resulting in a bigeminal pattern (Fig. 4). The results of the electrophysiological studies are shown in the Table.

Case 2

The first patient's mother had been followed by a local hospital for 'left ventricular enlargement, idioventricular rhythm and possible auricular block'. She had been asymptomatic until the age of 16 years when she started having episodes of light-headedness associated with exertion. On physical examination at the age of 19, the pulse was again noted to be irregular and slow (40/min) and a harsh nonradiating systolic murmur was present along the lower left sternal border as well as the apex; a soft mid-diastolic rumble and a wide, but physiologically split S2 was heard. Chest radiograph showed slight cardiomegaly with prominent pulmonary vasculature. Available electrocardiograms taken annually from 1953 to 1956 show junctional rhythm at a rate of 38/min and occasional sinoatrial impulses capturing the ventricles, with varying degree of aberrant conduction. The T waves were inverted in

TABLE Results of electrophysiological studies of Case 1

	Before atropine	After atropine (1 mg IV)
Basic cycle length	1500 ms (40/min)	890 ms (67/min)
AH interval of sinus beat	140 ms	88 ms
HV interval of sinus beat	36 ms	28 ms
Atrial pacing at cycle length of 600 ms		
Sinus escape time	3200 ms	1500 ms
His escape time	1360 ms	778 ms
AV node refractory period		
Functional	420 ms	
Effective	250 ms

FIG. 3 Simultaneously recorded limb leads I, II, and III of Case 1 after administration of atropine; both the junctional and the sinus rate increased, with the latter capturing the ventricles with varying degree of aberrancy.

the praecordial leads. Atropine increased both the sinus and junctional rate to 49/min resulting in a bigeminal (sinus-ventricular) pattern with higher degree of aberrant conduction than at rest. This patient continued to have exertional dizziness, and in March of 1964 she committed suicide at the age of 27.

Case 3

The maternal uncle of Case 1 was a 28-year-old man who had been seen since his childhood by a local hospital for 'cardiac enlargement and interference dissociation'. He was known to have bradycardia from the age of 3. At the age of 19, he started having episodes of exertional dizziness, and at the age of 26 he developed syncopal episodes. Six months before being seen, he sustained multiple fractures in an accident and is now confined in a total body cast. On physical examination, the pulse was irregular and slow at 52/min, a 3/6 systolic ejection murmur was maximally heard along the upper left sternal border, a 2/6 mid-diastolic murmur was heard at the 3rd left intercostal space. The second was wide but physiologically split.

Chest radiograph revealed a cardiothoracic ratio of 13/25.5 cm, without any specific chamber enlargement; the hilar areas and the central pulmonary vascular markings were prominent. Annual electrocardiograms since the age of 9 (1956) showed a junctional rhythm at a rate of 40/min, and occasional sinus impulses capturing the ventricles with varying degrees of aberrant conduction.

The mother's sister and the maternal grandfather of the first patient also had sinus bradycardia.

Discussion

The physical findings in these patients are very similar; slow irregular pulse, forceful left ventricular impulse, harsh ejection murmur, and mid-diastolic murmur. Long cardiac cycle lengths are associated with increased atrial pressure, ventricular end-diastolic volume, and stroke volume (Tavel, 1967b). The diastolic murmur and systolic ejection murmur may result from an increase of forward blood flow, with a high velocity through the semilunar valves or the atrioventricular valves in the absence of organic stenosis (Tavel, 1967a).

Long cardiac cycle length and the associated increase in intracardiac volume can influence the cardiothoracic ratio on the chest radiograph as well as the ventricular repolarization process resulting in T wave changes of the 'volume over-load pattern'.

Bacos, Eagan, and Orgain (1960) reported the first series of familial nodal rhythm. No apparent cause was found in these patients. Spellberg (1971) reported another family with sinus node dysfunction. In both these families inheritance appears to

be Mendelian dominant. This is true in our series as well.

In adults, ischaemic heart disease with involvement of the sinus node artery and degenerative changes of the sinus node have been proposed as a possible aetiology of the sick sinus node syndrome (Ferrer, 1968, 1973). Abnormalities of the sinus node artery and infarction of the sinus node have been suggested by James as a possible aetiology of congenital sinoatrial and atrioventricular block (James, 1964, 1967). However, recent coronary

FIG. 4 His bundle electrogram. The top panel shows the basic rhythm. The lower panel is an example of the rhythm after administration of atropine. From top to bottom (upper panel): leads III and I of the surface electrocardiogram, high right atrial electrogram (HRA), His bundle electrogram (HBE), 10 ms time lines (T). H=His deflection. V=ventricular electrogram. A=atrial electrogram. The same sequence and abbreviations are used for the lower panel. In the basic rhythm, note each QRS complex is preceded by a His deflection and has a normal HV interval. Atrial electrogram follows the QRS complex confirming that the basic rhythm originates from a junctional pacemaker. Lower panel shows the rhythm after administration of atropine; the first and the third beat originate in the sinus node as shown by an upright P wave on the surface electrocardiogram and a high-low relation of the atrial electrograms. The second beat is a junctional beat similar to that of the basic rhythm.

artery studies by Engel *et al.* (1975) in patients with sick sinus node syndrome showed no abnormality of the sinus node artery. These authors could not exclude small vessel disease, but they concluded that coronary artery sclerosis of the sinus node artery was probably not related to the sick sinus node syndrome. If this is true for adult patients with sick sinus syndrome, ischaemic heart disease as an aetiology for familial sinus node dysfunction is extremely unlikely. Most of the patients with familial sinus node dysfunction reported developed this disorder at a very young age. In 2 of our patients sinus node dysfunction was noted at the age of 3, an unlikely age for ischaemic heart disease.

Sinus node dysfunction may occur as a result of congenital structural abnormality (James, Froggatt, and Marshall, 1967). Such abnormalities have also been seen in patients with familial atrioventricular block (James, McKone, and Hudspeth, 1975). The aetiology of these abnormalities is not clear. One wonders whether these changes could be the result of a persistent increase in vagal tone for a long period of time. Such an increase in the vagal tone for a prolonged period may result in failure of response of the P cells of the sinus node very similar to an end organ failure. In all of our patients there was evidence of increased vagal tone. All of them had pronounced sinus bradycardia as the first feature of the sinus node dysfunction and in Case 1 sinus node recovery time and the frequency of the sinus node were improved after intravenous atropine, indicative of persistent increase in vagal tone. Vagotonia was reported as a rare cause of physiological bradycardia in healthy young adults (Dighton, 1974).

Changes in the autonomic tone have been shown to occur in other familial electrocardiographic abnormalities. An example is the familial QT prolongation with or without deafness (Jervell and Lange-Nielsen, 1957; Ward, 1964). In this syndrome of prolonged QT, the QT interval can be shortened with stimulation or blocking of one or the other sympathetic chain (Moss and McDonald, 1971; Vincent *et al.*, 1974). In this condition, the recovery phase of the ventricle is prolonged as shown by the long QT interval. Experimental data from the dog and data from patients suggest that recovery phase of the ventricle is dependent on the sympathetic tone (Yanowitz, Preston, and Abildskov, 1966; Blatt, Abildskov, and Burgess, 1974). The basic mechanism of familial QT prolongation may then be an altered sympathetic tone.

It appears that familial increase in vagal or sympathetic tone may result in distinct clinical entities. An increase in vagal tone may result in familial sinus node dysfunction. The patients with

familial sinus node dysfunction at a later stage may become symptomatic with bradycardia. Bradycardia may respond to a long-acting vagolytic agent or may require a demand pacemaker. If these patients develop tachyarrhythmias suppressive antiarrhythmic drugs in addition to pacing may be indicated.

References

- Bacos, J. M., Eagan, J. T., and Orgain, E. S. (1960). Congenital familial nodal rhythm. *Circulation*, **22**, 887.
- Blatt, S. J., Abildskov, J. A., and Burgess, M. J. (1974). The mechanism of paradoxical QT interval changes with sympathetic manipulation. *Circulation*, **50**, Suppl. 3, 216.
- Dighton, D. H. (1974). Sinus bradycardia; autonomic influences and clinical assessment. *British Heart Journal*, **36**, 791.
- Engel, T. R., Meister, S. G., Feitosa, G. S., Fischer, H. A., and Frankl, W. S. (1975). Functional appraisal of sinus node artery disease. *American Journal of Cardiology*, **35**, 135.
- Ferrer, M. I. (1968). The sick sinus syndrome in atrial disease. *Journal of the American Medical Association*, **206**, 645.
- Ferrer, M. I. (1973). The sick sinus syndrome. *Circulation*, **47**, 635.
- James, T. N. (1964). An etiologic concept concerning the obscure myocardiopathies. *Progress in Cardiovascular Diseases*, **7**, 43.
- James, T. N. (1967). Congenital deafness and cardiac arrhythmias. *American Journal of Cardiology*, **19**, 627.
- James, T. N., Froggatt, P., and Marshall, T. K. (1967). Sudden death in young athletes. *Annals of Internal Medicine*, **67**, 1013.
- James, T. N., McKone, R. C., and Hudspeth, A. S. (1975). De subitaneis moribus; X Familial congenital heart block. *Circulation*, **51**, 379.
- Jervell, A., and Lange-Nielsen, F. (1957). Congenital deaf-mutism, functional heart disease with prolongation of the Q-T interval, and sudden death. *American Heart Journal*, **54**, 59.
- Mandel, W., Hayakawa, H., Danzig, R., and Marcus, H. S. (1971). Evaluation of sino-atrial node function in man by overdrive suppression. *Circulation*, **44**, 59.
- Moss, A. J., and McDonald, J. (1971). Unilateral cervico-thoracic sympathetic ganglionectomy for the treatment of long QT interval syndrome. *New England Journal of Medicine*, **285**, 903.
- Narula, O. S., Samet, P., and Javier, R. P. (1972). Significance of the sinus-node recovery time. *Circulation*, **45**, 140.
- Scherlag, B. J., Lau, S. H., Helfant, R. H., Berkowitz, W. D., Stein, E., and Damato, A. N. (1969). Catheter technique for recording His bundle activity in man. *Circulation*, **39**, 13.
- Spellberg, R. D. (1971). Familial sinus node disease. *Chest*, **60**, 246.
- Tavel, M. E. (1967a). *Clinical Phonocardiography and External Pulse Recordings*, p. 134. Year-Book Medical Publishers, Chicago.
- Tavel, M. E. (1967b). *Clinical Phonocardiography and External Pulse Recordings*, p. 125. Year-Book Medical Publishers, Chicago, Illinois.
- Vincent, G. M., Abildskov, J. A., Burgess, M. J., and Millar, K. (1974). Autonomic manipulation in the inherited long

- QT-recurrent syncope syndromes. *American Journal of Cardiology*, **33**, 174.
- Ward, O. C. (1964). A new familial cardiac syndrome in children. *Journal of the Irish Medical Association*, **54**, 103.
- Yanowitz, F., Preston, J. B., and Abildskov, J. A. (1966). Functional distribution of right and left stellate innervation to the ventricles: production of neurogenic electro-

cardiographic changes by unilateral alteration of sympathetic tone. *Circulation Research*, **18**, 416.

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