Histopathological correlates of sinoatrial disease¹

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SUMMARY Six hearts from patients suffering from rhythm disorders consistent with the diagnosis of sinoatrial disease were histologically examined. Four of the patients had shown a tachycardia-bradycardia syndrome, and the remaining two patients episodes of sinus arrest or sinoatrial block with a slow junctional escape rhythm. The rhythm disorders had occurred in the setting of chronic sinoatrial disease (3 cases), acute myocardial infarction (2 cases), and diphtheritic myocarditis (1 case).

The abnormalities which were more consistently observed consisted of (1) total or subtotal destruction of the sinus node (6 cases); (2) total or subtotal destruction of the areas of nodal atrial continuity (5 cases); (3) inflammatory or degenerative changes of the nerves and ganglia surrounding the node (6 cases); (4) pathological changes in the atrial wall (5 cases). Chronic or acute lesions involving the AV node, the bundle of His, and its branches or their distal subdivisions were also found in all 6 hearts.

The relationship between the observed pathological changes and the physiological disorders are discussed.

The clinical profile (Short, 1954; Birchfield *et al.*, 1957; Ferrer, 1968; Rosen *et al.*, 1971; Rubenstein *et al.*, 1972; Kaplan *et al.*, 1973; Kulbertus *et al.*, 1973; Guntner *et al.*, 1976) and electrophysiological behaviour (Mandel *et al.*, 1972; Narula *et al.*, 1972; Strauss *et al.*, 1973) of patients with sinoatrial disease have received much attention in recent years. It is well established that the various components of the syndrome may occur not only chronically but also more acutely, as in myocardial infarction or toxic myocarditis. We have examined histologically the sinoatrial region and conducting system in 6 hearts from patients with sinoatrial rhythm disorders; 3 were chronic cases, 2 had a myocardial infarction, and 1 a diphtheritic myocarditis. The histological findings are reported and an attempt has been made to correlate the observed alterations with the physiological disorders.

Techniques

In each case, the sinoatrial node, nodal atrial junction, atrial myocardium, sinus node artery, and

nervous structures were studied. In addition, the specific tissue of the atrioventricular junction was also carefully examined.

SINOATRIAL REGION

The region of the sinoatrial node was obtained in the following manner. A cut was first made from the orifice of the inferior vena cava to the upper part of the right atrial appendage. The second cut passed behind the right atrial appendage and was directed towards the orifice of the superior vena cava; finally, a third cut went from the superior to the inferior vena cava, thus separating a block which was fixed in formalin and embedded in paraffin. 10 μ sections were prepared parallel to the long axis of the sinus node. Each fortieth section was stained with haematoxylin and eosin, Azan-Heidenhain's solution, or Masson's trichrome. Furthermore, in each case, 20 to 40 sections were stained by orcein or Congo Red in order to study the pathological changes in elastic fibres and to identify amyloid deposits. Bodian's staining was used to study the nervous structures.

The following morphological criteria were used.

Sinoatrial node

Severe fibrosis was diagnosed when only a few scattered nodal cells remained, embedded in a mass of collagen tissue.

¹The data reported in this paper were included and briefly described in the proceedings of a Symposium on Reentrant Arrhythmias held in Liège in 1976 (Demoulin, J. Cl. and Kulbertus, H. E. Pathological correlates of atrial arrhythmias in reentrant arrhythmias, mechanisms and treatment. H. E. Kulbertus, Ed. MTP Lancaster, p. 99, 1977).

Fig. 1 Case 5. An example of a sinus node which is severely involved by a fibrotic process. Only very few nodal cells remain (arrow); areas of lipomatosis can also be found close to the sinus node artery (san). (Azan $\times 60$.)

Nodal atrial junctions

We have never been able to demonstrate morphologically specialised atrial internodal pathways in the human heart (Janse and Anderson, 1974). However, areas of nodal atrial continuity are consistently seen along the margins of the compact sinus node (Truex, 1976). Such areas of blending of nodal and atrial muscle cells are notably found along the tail of the node, along its anterior aspect, and along its endocardial margins, the regions presumed to be the site of origin of the bundles described by Thorel (1909), Bachmann (1916), and Wenckebach (1906-1907) respectively. These areas most probably represent important structural bridges between the node and the atrial myocardium and were, therefore, carefully studied.

Atrial myocardium

The pathological changes in the atrial myocardium

were graded according to Bailey's classification (Bailey *et al.*, 1968): grade I, atrial myocardium grossly normal, or minimal changes only; grade II, moderate to severe fibrosis with preservation of muscle mass and architecture; grade III, extensive fibrosis with loss of muscle and architecture.

Ganglia and nerves

Chronic alterations of the nervous structures were identified from the description by Rossi (1969). The ganglia were thought to be abnormal when their cells showed vacuolar degeneration or atrophy and when there were changes in the pericellular processes or capsular cells. Haemorrhagic and inflammatory infiltrations of the nerves were also carefully looked for.

AV junctions

The AV node, the common His bundle, the left and right bundle-branches and their arborisations, were studied using the technique described by Lenegre (1955).

Results

Six hearts from patients with documented sinoatrial disease were studied. In 4 of the cases, the disease manifested itself by a tachycardia-bradycardia syndrome, and in the remaining 2 instances, there were episodes of sinus arrest or sinoatrial block, with slow junctional escape rhythm.

The significant clinical features and the gross necropsy findings are summarised in Table 1. Table 2 describes the histopathological changes observed in the sinoatrial region. The lesions seen within the AV node, common His bundle, and bundle-branches are listed in Table 3.

The abnormalities which were more consistently encountered were total or subtotal destruction of the sinus node (6 cases), total or subtotal destruction of the areas of nodal atrial continuity (5 cases), inflammatory or degenerative changes in the nerves and ganglia surrounding the node (6 cases), and grade III pathological changes in the atrial myocardium (5 cases). Chronic or acute lesions involving the AV node (Tawara), the bundle of His, its branches, or their distal subdivisions were also found in all 6 hearts.

Discussion

Very few reports relating the histopathological anomalies associated with the syndrome of sinoatrial rhythm disturbances have been published (Hudson, 1960; James and Birk, 1966; Rossi, 1969; Acar *et al.*, 1970; Rasmussen, 1971; Rosen *et al.*, 1971b;

Fig. 2 Case 4. A nerve close to the sinus node. Severe haemorrhagic infiltration of the nerve is easily recognised. (Azan $\times 60$.)

Kaplan *et al.*, 1973; Kulbertus *et al.*, 1973; Warembourg *et al.*, 1974). Two recent reports have appeared during the preparation of this paper. Thery *et al.* (1977) described their findings in a group of patients of whom 6 had a bradycardia-tachycardia syndrome, 12 had evidence of sinoatrial block, and 1 had permanent atrial standstill. Evans and Shaw (1977) also described the pathological data from 8 patients diagnosed during life as having chronic sinoatrial disorder. The results of these different studies were consistent: lesions of the sinus node and of the atrial wall were commonly found in sinoatrial disease.

The present investigation corroborates those findings and stresses two additional features. First, the structural bridges which connect the node to the common atrial myocardium seem to be frequently damaged in this clinical syndrome. Secondly, the nervous structures surrounding the node are also often the site of pathological changes.

It seems generally agreed that the syndrome under discussion comprises: (1) bradyarrhythmias with episodes of sinus bradycardia, sinus arrest or pauses, and/or sinoatrial block, (2) a reluctance of junctional escape pacemakers to emerge, and (3) in about two-thirds of cases, episodes of supra-ventricular, mainly atrial, tachyarrhythmias. Each of these three manifestations may be related to the anatomical abnormalities.

The bradycardic episodes may reflect reduced

sinus node automaticity or impaired conduction from the centre of the node to its periphery or from the node to the atrial myocardium. These disorders can surely be accounted for by the severe changes observed within the node itself, by the disruptive lesions located along the areas of nodal atrial continuity and, finally, by the pathological involvement of the perinodal nervous structures. Similar pathological features are sometimes seen though rarely, in individuals maintaining a normal sinus rhythm (Demoulin and Kulbertus, 1977). At present, the minimum number of functioning nodal cells needed to ensure the formation of a proper sinus impulse remains unknown. Furthermore, it seems well established that the distribution of pacemaker cells is not limited to the area of the node itself and that pacemaker cells can also be found around the node, more particularly towards the region of the crista terminalis. This might explain the persistence of a satisfactory sinus rhythm in some patients in spite of very severe intranodal fibrosis (Demoulin and Kulbertus, 1977; Thery *et al.*, 1977). This might also be the reason for apparently normal or very short sinoatrial conduction times recorded in patients with sinus node dysfunction (Strauss *et al.*, 1976).

The fact that a satisfactory junctional escape pacemaker may not always emerge might be accounted for by at least two different mechanisms. First, the AV junction is quite commonly the site

Fig. 3 Case 4. Haemorrhagic infiltration (arrow) is seen to interrupt a region of continuity between the sinus node (san) and the common atrial myocardium (cam). (Azan $\times 100$.)

of pathological changes in the disease under discussion. Furthermore, it has been shown that to ensure proper automatic function of the junctional pacemaker, a normal sympathetic input is essential (Millar *et al.*, 1972). The commonly observed abnormalities of the intracardiac ganglia may, therefore, play a very significant role.

The occurrence of tachyarrhythmias can also find a satisfactory explanation in the pathological observations. The disruptive lesions seen at the sinoatrial junctions and often at the level of the approaches to the AV node may favour the appearance of re-entrant beats or tachycardias (Narula, 1974; Weisfogel *et al.*, 1975; Wu *et al.*, 1975). The same holds true for the lesions in the atrial wall. The fibrotic scars, necrotic areas, and inflammatory or haemorrhagic infiltrations constitute obstacles to conduction which, in the thin atrial wall, delineate ideal paths for circus movement and re-entrant excitation and may thus set the stage for various tachyarrhythmias. In the present series, the atrial wall lesions usually consisted of fairly large areas of fibrosis, necrosis, or infiltration and it seems reasonable to imagine that they constitute anatomical obstacles favouring the development of paroxysmal atrial tachycardia which is known to be the most frequent rhythm disorder seen in this disease (Guntner *et al.*, 1976).

It seems, therefore, that sinoatrial disease is a clinical entity in which the correlation between the anatomical lesions and the physiological disturbances is clearly established (Kaplan *et al.*, 1973; Kulbertus *et al.*, 1973; Demoulin and Kulbertus,

Table 1 Summary of clinical details and necropsy findings

Case no.	Age (y)	Sex	Clinical data	Rhythm and conduction disturbances	Necropsy findings
1	63	M	Myocardial infarction	PSVT; SA with SEJR; transient 1st and 2nd degree AV block; RBBB	Enlargement of ventricular cavities; old anterolateral infarct; thrombosis of RCA, obstruction of CxA, and stenosis of LADA
2	28	M	Diphtheritic myocarditis; congestive heart failure	PAT; PAF; PAF1; SB and pauses; transient 3rd degree AV block; LPHB with RBBB	Both ventricles dilated
3	72	M	Coronary heart disease; ventricular arrhythmias	SB; SA with SEJR; PAF; PAT; ventricular bigeminy	Large anterior and apical scar extending inferiorly and surrounded by fresh necrotic tissue; LADA obstructed; CxA and RCA stenosed
4	75	F	Blood loss from gastrointestinal disease	PST; SB and SA	Ostium primum ASD; sarcoid granulomata in myocardium and mediastinal lymph nodes
5	66	F	Hypothyroidism; acute inferior infarction; Adams-Stokes attacks; cardiogenic shock	SB; SA with SEJR; transient 3rd degree AV block	Subacute inferior, apical, and postero-basal infarction; thrombosis of RCA
6	67	M	Congestive cardiomyopathy; syncopal attacks	PST; PAT; SA with SEJR; RBBB	Primary amyloidosis

PSVT, paroxysmal supraventricular tachycardia; PAF1, paroxysmal atrial flutter; SB, sinus bradycardia; RBBB, right bundle-branch block; LADA, left anterior descending artery; PAT, paroxysmal atrial tachycardia; PST, paroxysmal sinus tachycardia; SA, sinus arrest; LPHB, left posterior hemiblock; CxA, circumflex artery; PAF, paroxysmal atrial fibrillation; SEJR, slow escape junctional rhythm; RCA, right coronary artery.

Table 2 Summary of pathological findings in SA node region

Case no.	Sinus node	Nodal-atrial junctions			Perinodal ganglia and fibres	SA node artery	Atrial wall
		Anterior margin	Inferior margin	Endocardial margin			
1	Dense fibrosis (body and tail); haemorrhage (body and head)	Fibrosis	Haemor. infiltration	Haemor. infiltration	Infl. and haemor. infiltration	Intimal thickening	Foci of coagulation necrosis; myofibrillar degeneration and vacuolisation (grade III)
2	Dense fibrosis (body and tail); infl. infiltration (head)	Fibrosis	Fibrosis	Infl. infiltration	Infl. infiltration	N	Thrombosis of right atrial appendage
3	Severe fibrosis	N	N	N	Degeneration	N	Scars; diffuse fibrosis (grade III)
4	Dense fibrosis (body and tail); haemor. infiltration	Replaced by fibrosis	Moderate fibrosis	Interrupted (haemor. infiltration)	Degeneration; haemor. infiltration	N	Thrombosis of right atrial appendage; multiple scars (grade III)
5	Extensive fibrosis; areas of coagulation necrosis and inflammatory infiltration	Interrupted (fibrosis)	Interrupted (fibrosis)	Fibrosis and haemor. infiltration	Infl. infiltration	N	Areas of coagulation necrosis; myofibrillar degeneration and inflammation (grade III)
6	Amyloid deposits; dense fibrosis	Interrupted (fibrosis)	Subtotal destruction (fibrosis)	Interrupted (fibrosis)	Amyloidosis	Amyloid deposits in vascular wall	Amyloid deposits; severe fibrosis (grade III)

Haemor., haemorrhagic; Infl., inflammatory; N, normal.

Table 3 Summary of pathological findings in AV junction

Case no.	AV node	Common His bundle	Right bundle-branch	Left bundle-branch
1	—	Dense fibrosis	Almost total fibrosis	Mild fibrosis of initial portion; posterior radiation severely fibrosed
2	Dense fibrosis of node approaches; inflammatory infiltration in node	—	—	Dense fibrosis of posterior fascicle; inflammatory infiltration of anterior radiation
3	—	—	Mild fibrosis (initial portion)	Dense fibrosis of anterior radiation; mild fibrosis of posterior fascicle
4	Dense fibrosis; areas of myofibrillar degeneration	Dense fibrosis	Dense fibrosis	Dense fibrosis of posterior radiation
5	Coagulation necrosis	Dense fibrosis	Coagulation necrosis of 3rd position	Dense fibrosis of midseptal and anterior fibres; coagulation necrosis of posterior radiation
6	Amyloidosis; dense fibrosis	Amyloidosis and fibrosis	Amyloidosis with fibrosis	Amyloidosis and fibrosis

1977; Thery *et al.*, 1977). However, some patients with hearts showing anatomical changes like those described in this paper may be in sinus rhythm or may present with isolated chronic atrial fibrillation (Demoulin and Kulbertus, 1977; Thery *et al.*, 1977). Thus, the physiological disturbance cannot necessarily be predicted from the anatomical findings; there is no doubt that there is a need for further studies in this field.

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