Pathogenesis of atrial arrhythmias

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A method of examining the sinuatrial node histologically and of quantitating the histological features is described. The histology of the node is analysed statistically in 43 cases of sinus rhythm or absence of cardiac pathology at necropsy. This revealed changes in the amount of nodal fibres and connective tissue and in the nodal artery, with advancing age.

The histology of the sinuatrial node in groups of cases with various atrial arrhythmias and underlying pathology was studied statistically by comparing the histological features of the tissue with those in the control group. It was found that there was diminution of nodal tissue in three groups of cases with atrial fibrillation associated with ischaemic heart disease, hypertension, and rheumatic heart disease and in a fourth group with other arrhythmia.

The degeneration of the fibres within the sinuatrial node may also be associated with similar degeneration of the extranodal fibres, but this cannot be shown histologically. If so, these areas of degeneration may act as ectopic foci. In addition the loss of nodal fibres may impair the ability of the pacemaker to activate the surrounding atrium. In established atrial fibrillation, the incompetence of the sinuatrial node will account for the poor response to a DC shock.

In his St. Cyre's Lecture at the Royal Society of Medicine, Professor Hudson described the histology of the sinuatrial node in 65 pathological hearts (Hudson, 1960). In 15 cases in which an established arrhythmia, usually atrial fibrillation, was present, there was extensive damage of the sinuatrial (SA) node, with depletion and poor staining of the nodal tissue and an increase in connective tissue. As a result he felt that he was able to predict from the nodal histology which cases might have an arrhythmia, though in one instance with considerable evidence of nodal damage, sinus rhythm was present. In this study Hudson was not able to correlate the appearance of the node with increasing age as described by Lev (1954), who found an increase in connective tissue and an apparent loss of muscle fibres.

It is the purpose of this study to investigate the histological changes that occur in the sinuatrial node with advancing age, and to analyse the findings in cases with various atrial arrhythmias in an attempt to find a pathological basis for the arrhythmias.

Method

The technique of examining the SA node histologically is based upon that described by Hudson (1960) in which he identified the 'summit' of the right atrium as the landmark to the node. Vertical strips of tissue taken to include the summit will therefore contain a portion of the sinuatrial node. The formalin-fixed specimens were then processed in the routine manner and the paraffin-embedded sections stained with haematoxylin and eosin. A further section was also stained with Weigert's elastic tissue stain, counterstaining with van Gieson's picro-fuchsin.

For this study of the histology of the SA node, the section best displaying the tissue in each case was selected. The SA node is arranged around a nodal artery (Fig. 1). It is composed of small eosinophilic staining muscle fibres around which there is a fine meshwork of elastic fibres. Occasionally there is infiltration of fatty tissue into the epicardial aspect of the node. Also in this region ganglion cells and nerve fibres may be seen.

In this study an effort was made to quantitate the histological features of the SA node. Thus on examining the sections displaying the SA node best, the nodal tissue may have a normal complement of nodal fibres (++), a reduced number (+), or none (-). Similarly the elastic and fibrous tissue may be present in slight (+), moderate (++), or maximal (+++) amounts. It was also of interest to study the changes in the nodal artery as Gross, Epstein, and Kugel (1934) have demonstrated well-defined ageing changes in the myocardial arteries. In childhood there is a well-demarcated internal elastic lamina dividing the intima from the media (designated change 1). From 5 years onward this elastic lamina splits so that it appears thicker (change 2). During the

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first three decades there is hyperplasia of the small amount of longitudinal smooth muscle present in the intima, which mixes with the elastic tissue to form a layer of musculoelastic hyperplasia (change 3). In later years elastic fibres spread into the muscle of the media, as does the collagen tissue from the adventitia (change 4). Though these levels of change are well defined, they cannot by their nature have an equal statistical distribution.

The histology of each case was assessed as it was collected without a knowledge of the clinical details. Later the cases were sorted according to whether there was sinus rhythm or an atrial arrhythmia present during life. The results of the histological assessments in groups depending on the presence of ischaemic heart disease, hypertension, or rheumatic heart disease were then compared statistically with assessments made in cases where there was sinus rhythm during life or no significant cardiac pathology found, in patients of similar age (age comparison for all groups $P > 0.25$). This comparison was made by computer using an exact probability programme.

Results

A preliminary study of 43 cases with normal cardiac function aged 2–90 years was carried out. The histology of the SA node was assessed as described and the results analysed statistically to see if there were any significant changes with advancing age. Table 1 shows the number of cases with each level of change and the correlation coefficients of these histological features with increasing age. The results show a gradual but not significant loss of nodal fibres. There is a highly significant increase in elastic and adipose tissue with age, and also a significant increase in fibrous tissue. The changes in the appearance of the nodal

FIG. 1 The sinuatrial node is composed of small, paler staining muscle fibres, arranged around the nodal artery. From a 2-year-old child. (H. and E. $\times 70$.)

artery are highly significant. These findings form a baseline against which the pathological histology may be compared.

Cases with atrial fibrillation during life were studied in groups according to the cardiac pathology, such as ischaemic heart disease, hypertension, and rheumatic heart disease. A small group of cases with other electrocardiographic abnormalities was also studied. The histological assessments of the sinuatrial

TABLE 1 Ageing changes in sinuatrial node

Age groups	No. of cases/group	Histological assessments of sinuatrial node																	
		Amount of nodal tissue			Fibrosis				Elastosis				Fat		Nodal artery				
		—	+	++	—	+	++	++++	—	+	++	++++	—	+	1	2	3	4	
2-9	5	0	0	5	0	2	3	0	0	4	1	0	5	0	3	0	2	0	
10-19	5	0	4	1	0	0	5	0	0	4	1	0	5	0	3	1	0	1	
20-29	5	0	1	4	0	0	5	0	0	2	3	0	3	2	1	1	1	2	
30-39	5	0	0	5	0	3	2	0	0	3	2	0	4	1	1	0	3	1	
40-49	4	0	4	0	0	0	4	0	0	2	2	0	4	0	0	2	2	0	
50-59	5	0	2	3	0	0	4	1	0	0	4	1	3	2	0	1	4	0	
60-69	5	0	3	2	0	2	2	1	0	2	2	1	1	4	0	1	3	1	
70-79	4	1	3	0	0	0	3	1	0	0	4	0	2	2	0	0	3	1	
80-89	5	1	2	2	0	0	3	2	0	0	4	1	2	3	0	0	2	3	
Correlation coefficient		-0.2961			0.3311				0.5295				0.4556		0.4903				
Probability		0.05-0.1			0.02-0.05				<0.001				0.001-0.01		<0.001				

nodes in these groups were then compared with groups of similar age where sinus rhythm was present, and with the exact probability values in Table 2.

Cases of atrial fibrillation with ischaemic heart disease Of the 17 cases in this group, 12 had healed infarcts and in 5 there was recent infarction. Of the cases with recent infarcts, 2 were posterior in position and 3 anterior. The thrombotic occlusions in both of the posterior infarcts were situated 5 cm and 2 cm from the origin of the right coronary artery, probably distal to the origin of the sinuatrial nodal artery.

In cases with recent infarction, the necrosis affected the node as well, revealing areas of recent infarction in 2 cases, where there is focal haemorrhage into the nodal tissue and the epicardial fat (Fig. 2). The nodal fibres in parts of these nodes appear swollen and more eosinophilic, but no polymorph infiltration is seen. Apart from a few lymphocytes in the nodal tissue, the nodes in the other cases show a slight increase in connective tissue and a reduction of the muscular element. In the statistical comparison, the only highly significant finding is the reduction of nodal tissue. Despite the appearance of the tissue in many of these cases, there is no statistical increase in connective tissue, nor is there accentuation of the ageing changes in the nodal artery.

Cases of atrial fibrillation with hypertension All 6 cases in this group had systemic hypertension and 5 died from a complication of this. The histology of the sinuatrial node when compared with that of the

FIG. 2 Areas of recent infarction are present in the sinuatrial node with focal haemorrhage into the tissue. From a 90-year-old man. (H. and E. $\times 80$.)

control group does not show any statistically significant change, though there is a slight reduction in nodal tissue. The nodal artery does not demonstrate any medial hypertrophy nor do the arterioles in the node appear thickened.

Cases of atrial fibrillation with rheumatic heart disease The 18 cases in this group all had mitral stenosis, 4 of them having

TABLE 2 Comparison of sinuatrial nodal histology in cases with atrial arrhythmias and sinus rhythm

Arrhythmia and underlying pathology	No. of cases		Histological comparisons and exact probability values																	
	Arrhyth- mia	Sinus rhythm	Amount of nodal tissue				Fibrosis				Elastosis				Fat		Nodal artery			
			-	+	++		-	+	++	+++	-	+	++	+++	-	+	1	2	3	4
Atrial fibrillation with ischaemic heart disease	17	14	8	9	0	0	0	10	7	0	2	11	4	5	12	0	2	8	7	
			2	8	4	0	2	8	4	0	2	10	2	5	9	0	1	8	5	
			P=0.02			P=0.39				P=0.86				P=0.72		P=0.88				
Atrial fibrillation with hypertension	6	19	3	3	0	0	1	5	0	0	0	6	0	3	3	0	2	3	1	
			2	10	7	0	2	12	5	0	2	14	3	9	10	0	2	12	5	
			P=0.08			P=0.37				P=0.73				P=1.00		P=0.44				
Atrial fibrillation with rheumatic heart disease	18	28	5	13	0	0	0	12	6	0	3	10	5	7	11	1	1	9	7	
			2	14	12	0	4	18	6	0	7	18	3	16	12	1	4	15	3	
			P=0.00			P=0.26				P=0.36				P=0.36		P=0.20				
Other atrial arrhythmias	8	14	4	4	0	0	1	2	5	0	3	4	1	4	4	0	0	5	3	
			1	8	5	0	2	9	3	0	2	10	2	7	7	0	2	10	2	
			P=0.02			P=0.12				P=0.57				P=1.00		P=0.66				

had a valvotomy. The other valvular deformities were mitral incompetence (5 cases), aortic stenosis (5 cases), aortic incompetence (3 cases), and tricuspid disease (4 cases).

No Aschoff bodies are seen in the nodal tissue or in relation to the atrial endocardium; however lymphocytes are frequently seen dispersed through the node, with aggregations in the epicardial fat related to fibrous thickening of the pericardium. The statistical comparison of the histology reveals a highly significant loss of nodal fibres without an increase in connective tissue. The nodal artery does not show any difference in the ageing changes.

Cases with other atrial arrhythmias In none of the 8 cases in this group was atrial fibrillation seen to supervene. The arrhythmias included frequent atrial ectopic beats (3 cases), supraventricular tachycardia (4 cases), and atrial flutter (1 case). The cardiac pathology in these cases was similar to the previous groups, 2 having ischaemic heart disease and 3 hypertension. Another case was a 13-year-old girl who developed a congestive cardiomyopathy of possible viral aetiology.

The most striking histological finding in one of these cases is the presence of an infiltration of squamous carcinoma in the nodal tissue (Fig. 3), with considerable destruction of the node. When the histology is compared statistically, the exact probability values show a significant decrease in the amount of nodal tissue, but no change in the connective tissue component or in the nodal artery is detected.

Discussion

Analysis of the findings in the sinuatrial node in normal controls at different age periods shows that there is a quantitative change in the histological features with advancing age. These findings agree with those of Lev (1954) with regard to the gradual increase in the amount of collagen, elastic and fatty tissue in the node. By the age of 40 he considered that the muscle and interstitial elements were present in about equal amounts; however after 60 years no further significant change took place. Lev did mention a diminution of nodal tissue but did not comment on the changes of the nodal artery.

In patients with atrial arrhythmia during life, irrespective of the cause, the most consistent histological change is shown to be a loss of nodal fibres. This was not accompanied by either an increase in connective tissue or accentuation of the ageing changes in the nodal artery. The decrease in the amount of nodal tissue is probably a degenerative pro-

FIG. 3 There is considerable destruction of the sinuatrial node due to infiltration of secondary squamous carcinoma. From a 78-year-old man. (H. and E. $\times 70$.)

cess, rather than the result of local inflammation when fibrosis would be present. In the sinuatrial node it is possible to gauge the relative amount of nodal tissue because of network of elastic tissue. Unfortunately with atrial muscle it is not possible to detect a loss of muscle fibres, as it does not have the intimate elastic supporting tissue.

The current physiological view for explaining the mechanism of the atrial arrhythmias assumes a unifocal or multifocal pacemaker in the atrium (Prinzmetal *et al.*, 1950). These ectopic pacemakers are considered to be areas of 'injured' muscle fibres with enhanced automaticity, the type of arrhythmia produced depending on the rate of discharge. Burn (1960) stressed the importance of a shortened refractory period, as when there is vagal stimulation, so that stimulation of the atrial muscle will result in fibrillation. From the results of the present study it seems that the changes in the sinuatrial node in atrial tachycardia, flutter, or fibrillation may be of equal importance to the ectopic pacemakers in the atrial myocardium, and to the various factors that affect its refractoriness. The degenerative process in the node may also be proceeding in the atrial muscle, perhaps giving rise to the ectopic pacemakers. Hudson (1960) noted that the sinuatrial node was usually destroyed along with the atrial muscle in cases of rheumatic heart disease and myocardial infarction.

The onset of atrial fibrillation may complicate myocardial infarction in 10 per cent of cases (James, 1961). This author examined 11 cases: in each he found an occlusion in the coronary artery from which the nodal artery originated, and evidence of recent infarction in the node. Like the two cases described in this study, James noted infarction in the periphery of the node, with haemorrhage into the epicardial fat. He discussed the various factors present in acute myocardial infarction which may lead to atrial fibrillation such as depression of sinuatrial nodal function due to ischaemia, increase in vagal tone, or impaired conduction of the impulse from the node due to infarction of the surrounding atrial muscle and haemorrhage. In an experimental study (James and Hershey, 1962), atrial fibrillation could not be produced by ligating the sinuatrial nodal artery in 5 dogs, though when there was accompanying vagal stimulation (produced reflexly by injecting catecholamines), fibrillation occurred. How important these factors are in man is not known, but ischaemia of the atrial muscle (as well as the sinuatrial node), and alternation in refractoriness of the atrial muscle are likely to be significant.

The extensive destruction of the sinuatrial node in these cases with established atrial fibrillation will mean that the node may be incapable of generating a sufficient activating potential to stimulate the surrounding atrial muscle. The probable loss of pacemaking function would account for the failure of the heart to maintain sinus rhythm for long in cases of established atrial fibrillation, after a

DC shock (Halmos, 1966). This finding would also suggest that atrial pacing may be helpful in correcting some of the atrial arrhythmias.

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