Atrioventricular nodal function in progressive systemic sclerosis: electrophysiological and morphological findings

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SUMMARY Electrophysiological data consistent with atrioventricular nodal dysfunction were obtained in 10 out of 19 patients with progressive systemic sclerosis (scleroderma). Conducting system studies were carried out in a further seven patients with progressive systemic sclerosis. In each the proximal portion of the atrioventricular node was consistently found to be smaller and more slender. It is postulated that there is a relation between proximal atrioventricular nodal structural alterations and impaired atrioventricular nodal function.

Conducting system disorders are found in progressive systemic sclerosis.¹⁻³ First degree atrioventricular block occurred in as many as 20 per cent of patients in one of these series² and in all three series there was at least one case with complete atrioventricular block. In an additional case of progressive systemic sclerosis with complete heart block, at necropsy the atrioventricular node was found to be fused with the central fibrous body of the heart. At the bifurcation of the bundle there was an acute degenerative change and there was fibrosis of the right bundle.⁴ In a necropsy study of eight further patients James⁵ observed that before death at least five of them had had significant conducting system disease localised at the atrioventricular node or bundle of His, as judged by the electrocardiogram, and that in each there were severe morphological abnormalities present at these sites and at the sinus node. He felt that the normal difference in collagen content between the sinus node on the one hand and the atrioventricular node junctional tissues on the other may partially explain why fibrosis was so much more conspicuous in the former. He concluded that a combination of sinus node destruction and excess focal fibrotic partitioning in the atrioventricular junction was the likely basis for a high frequency of paroxysmal supraventricular tachycardia, the electrophysiological consequences being failure of normal automaticity together with the availability of multiple anatomical routes for atrioventricular junctional re-entry. Though the series of Ridolfi

and colleagues⁶ contained three patients with first degree heart block and one with complete block on the electrocardiogram, at necropsy no significant atrioventricular nodal disease was found. Recently, however, in a necropsy specimen of the atrioventricular node in a patient with progressive systemic sclerosis, we found that there was loss of tissue at the proximal end of the structure. Because of the discrepancy of the findings in the published reports, the present study was undertaken to confirm this morphological observation of ours and to examine atrioventricular nodal function to see how reliable the electrocardiogram was in identifying atrioventricular nodal disease.

Subjects and methods

The last seven patients who died at the ULCA Medical Center with the diagnosis of progressive systemic sclerosis were studied. After a routine necropsy, the conducting system, including the atrioventricular node, atrioventricular bundle, and bundle-branches were removed in a single block. The blocks were processed in the manner previously described.⁷ This, in brief, involved sectioning at 5 μ intervals and retention of every fifth section. These sections were made longitudinally parallel to the atrioventricular node and bundle and mounted three to a slide. Alternate slides were stained with haematoxylin, phloxine, and tartrazine.

By sectioning the atrioventricular node and bundle in a direction longitudinally parallel rather than at right angles to the conducting tissue,

complete sectioning of the structures was achieved in fewer sections than in the traditional method.⁸ This enabled us to compare more similar sections by relating them to the distance from the right atrial endocardium than other more arbitrary methods.

For the electrophysiological studies of atrioventricular nodal function 19 patients with progressive systemic sclerosis being followed in the Division of Rheumatology at UCLA were prospectively studied by a right heart catheterisation between August 1977 and January 1979. Eighteen of the patients met the criteria of the American Rheumatism Association⁹ for scleroderma and one patient had the syndrome of calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly, and telangiectasia.¹⁰ The mean age of the patients was 52 years and the average duration of the disease was 12 years. The procedure for the studies was approved by the UCLA Human Subject Protection Committee and fully informed consent was obtained from all the subjects.

The PR interval was obtained from the surface leads and the atrioventricular nodal conduction time (AH interval) was measured during the same cardiac cycles. Right atrial pacing was performed until second degree heart block occurred. The effective and functional refractory periods were measured by pacing the atrium at a standard cycle length of 590–620 ms and applying an extra stimulus every eighth complex. Patients in whom no response was provoked had refractory period measurements made by applying an extra stimulus after every eighth spontaneous beat (cases 4, 11, 12). One patient had a sinus tachycardia and was paced with a cycle length of 500 ms (case 16) and in case 17 refractory period measurements were not obtained at the standard cycle length but were obtained at a paced cycle length of 680 ms.

Results

CLINICAL AND ELECTROPHYSIOLOGICAL FINDINGS

In five of the seven patients who died electrocardiograms immediately before death showed no specific conduction system disorder. One patient had complete atrioventricular block and the last a prolonged PR interval.

Electrocardiographic and electrophysiological data relating to atrioventricular function in the 19 patients are listed in Table 1. Two patients had prolonged PR intervals and prolonged atrioventricular nodal (AH) conduction times (cases 12, 19). A further patient (case 10) had a prolonged atrioventricular nodal conduction time which was

not reflected in a prolonged PR interval. Two patients had atrioventricular nodal conduction times of 70 ms or less (cases 2, 17) and a further two (cases 1, 16) had conduction times close to this. The refractory period measurements of the atrioventricular node disclosed that eight patients had abnormally prolonged intervals (cases 4, 11, 12, 14, 15, 16, 18, 19). The response of atrioventricular nodal conduction to atrial pacing is illustrated in Fig. 1. Cases 12 and 19 showed a rather straight incremental change in atrioventricular nodal conduction, unlike the more usual exponential increase in conduction time with decrease in cycle length. Cases 16 and 17 had a relatively slight incremental change in atrioventricular nodal conduction from the longer cycle lengths of 500 to 300 ms in case 16 and from 675 to 375 in case 17. The other measurements of cycle length in these cases were around 300 ms with AH intervals of between 100 and 120 ms.

While it is quite possible that these data are incomplete it is possible that at the shorter cycle lengths conduction was down pathways with a

Table 1 Measurements of atrioventricular nodal function (ms)

Case no.	Cycle length (ms)	PR interval	AH interval	Paced cycle length	AV node	
					ERP	FRP
1	780	150	75	600	280	350
2	680	160	70	600	320	360
3	833	165	100	590	340	350
4	833	175	115	600 and 850*	300*	360*
5	706	190	105	610	320	360
6	840	180	110	590	220	300
7	857	200	115	590	320	350
8	857	175	115	600	350	370
9	706	155	90	600	230	340
10	760	185	135	600	240	300
11	720	190	90	600 and 740*	410*	740*
12	1000	235	180	600 and 930*	440*	940*
13	840	180	90	610	380	390
14	667	155	85	600	240	540
15	833	160	80	600	300	540
16	600	135	75	—	—	—
17	800	150	65	500†	280	340
18	800	180	110	620	340	520
19	680	220	125	600 and 680‡	340†	540†
Normal		≤200	≤120	600	≤400	≤500

* Spontaneous cycle length and refractory period measurements (at the paced cycle lengths the atrioventricular node was entirely refractory).

† Longer cycle length at which overdrive of sinus tachycardia was possible.

‡ Second paced cycle length.

ERP, effective refractory period. FRP, functional refractory period.

longer conduction time but shorter refractory periods.

MORPHOLOGICAL FINDINGS

The seven patients in whom the heart was available for study all had had progressive systemic sclerosis with involvement of the lungs, skin, and gastro-intestinal tract for a number of years. Table 2 lists the cardiac lesions found in these patients.

In the conducting system, the atrioventricular nodes were remarkably similar in all seven cases. Instead of the normal appearance of a rather pear-shaped proximal atrioventricular node (Fig. 2a) the proximal part of the node was slender and nearly the same diameter as the distal part (Fig. 2b). The nodal structure did contain more fibrous tissue in the patients who had progressive systemic sclerosis, but this was only apparent, however, when age-matched controls were studied. In one case (Fig. 3) there clearly was discontinuity between the proximal portion of the atrioventricular node, and the distal portion and atrioventricular bundle.

Table 2 Cardiac involvement in progressive systemic sclerosis

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Pericardial effusion	+	+	+	+	+	+	+
Intimal proliferation of the arteries	+	+	+	+	+	+	+
Scleroderma cardiomyopathy		+					
Area of focal necrosis							+
Right ventricular hypertrophy			+	+	+		
Atrioventricular node abnormalities	+	+	+	+	+	+	+

Fig. 1 Atrial pacing to second degree heart block in 19 patients with progressive systemic sclerosis. The cycle length (ms) is plotted against the atrioventricular conduction (A-H). Cases 12 and 19 have a long conducting interval and straight curve. Cases 2, 16, and 17 have abnormal curves, the latter two with broken curves which are consistent with dual atrioventricular nodal pathways.

Fig. 2 (A) A normal atrioventricular node (AN) can be seen between the atrial (AT) and the ventricular (VM) muscle. The proximal node, at the end of the structure, is surrounded by collagenous tissue (pale staining). Along the entire course of the node this tissue separates the node from both atrium and ventricle. As the node is followed distally (toward the right) it blends into the atrioventricular bundle (AB). (Haematoxylin, phloxine, and tartrazine $\times 6$ original magnification.) (B) In contrast, a typical atrioventricular node and atrioventricular bundle of a patient with progressive systemic sclerosis. The node is flattened and narrow, particularly in the proximal area. (Haematoxylin, phloxine, and tartrazine $\times 6$ original magnification.)

In this case there had been complete heart block with narrow QRS complexes on the electrocardiogram for several years.

The proximal portion of the right bundle-branch was normal in both branching pattern and structure except in the case with complete heart block, in which it was large but could not be traced back to the common bundle. The branching patterns of the proximal portions of the left bundle appeared normal in all the cases except the one in which there was complete heart block. The left bundle emerged from the common bundle over a relatively wide area.

Discussion

The advantage of our technique in sectioning the atrioventricular node is threefold. Firstly by doing so parallel to the long axis we cut through about a millimetre of right ventricular endocardium and then through the one and half millimetres of node. Thus an entire atrioventricular node and bundle study is contained in many fewer sections. Traditional methods section at right angles to the long axis and the node, bundle, and origin of the bundle-branches is nearly 15 mm long, as opposed to 1.5 mm in the plane in which we section. Secondly we can more easily compare sections from different subjects by using the right-sided endocardial surface as a reference point. We can then measure accurately the distance from the surface to the conducting system structures. The third advantage is that in the particular plane in which we view the structures we can in appropriate section see the outline of the node, bundle, and part of the branching system. This technique does not jeopardise, however, microscopical analysis.

We found that in one case there was discontinuity between the penetrating portion of the atrioventricular node and bundle. This discontinuity was probably the cause of the clinical finding of complete heart block in this case. All the cases, however, showed a remarkably consistent finding—namely, that while the microscopical structure of the proximal atrioventricular node appeared to be within normal limits, the macroscopical appearance was not. The normally bulbous, pear-shaped proximal end was long and narrow.

We believe that this is probably a manifestation of progressive systemic sclerosis. There is no doubt that the patients had the disease for long periods and that, as shown in Table 2, the heart was involved in all of them.

We also have electrocardiographic evidence that in two of these seven cases there was evidence of atrioventricular block, though we cannot unequivocally attribute the block to the morphological change seen in the atrioventricular node. Certainly in the single patient with complete block there was other histological evidence, the discontinuity between the node and the bundle, but this patient, too, had a narrow proximal portion of the node. The other six all had abnormal nodes but only one had a prolonged PR interval and it was for this reason we undertook a parallel study to look for more subtle evidence of atrioventricular nodal damage. The 12 lead electrocardiogram is inadequate in this respect, for though a long PR interval may indicate atrioventricular nodal disease, a long intra-atrial conduction time and a long His to Purkinje conduction time may also be responsible for this.¹¹ Indeed, a prolonged atrioventricular nodal conduction time can be masked by a short His-Purkinje conduction time and thus give a normal

Fig. 3 The atrioventricular nodal area and atrioventricular bundle (AB) in a patient with progressive systemic sclerosis and complete heart block. The proximal atrioventricular node (P-AN) has degenerated. The distal atrioventricular nodal (D-AN) area is well formed and blends into the atrioventricular bundle. Ventricular muscle (VM) is seen inferiorly to the node. (Haematoxylin, phloxine, and tartrazine. Original magnification $\times 12$).

PR interval.¹² In fact we found that eight of the nineteen patients had impaired atrioventricular nodal conduction and a further three had conduction which was at the upper limits of normal. Two other patients, however, had an abnormally brief conduction time through the atrioventricular node.

It is uncertain whether both the decreased and the enhanced conduction can be explained by the change we describe in the proximal portion of the node. In the rabbit's atrioventricular node, a structure similar to the human one, the greatest conduction delay occurs in the most proximal portion.¹³ The major morphological changes in the atrioventricular node that we have observed are in the proximal region. Thus a reduction in the size of this area by fibrous replacement may cause relatively quicker atrioventricular nodal conduction, when conduction is intact, because of the reduction of the slowest area of conduction. Increased fibrosis around the proximal end of the atrioventricular node may also be responsible for the relatively common finding of prolonged atrioventricular nodal conduction or prolonged atrioventricular nodal refractory periods. The milieu in which enhanced and slowed atrioventricular nodal conduction occurs may be conducive to tachyarrhythmias. Indeed, James⁵ speculates that atrioventricular nodal changes could be responsible for a high frequency of supraventricular tachycardias.

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