Pharmacological observations in patients with nodoventricular pathways

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SUMMARY Three patients with accessory nodoventricular pathways and re-entry tachycardia are reported. In all three patients the accessory nodoventricular pathway formed the anterograde limb of the re-entry circuit while the His-Purkinje-atrioventricular node axis formed the retrograde limb of the tachycardia in two of the patients and a concealed accessory pathway formed the retrograde limb in the remaining patient. All three patients also manifested dual anterograde atrioventricular nodal pathways with conduction through the accessory nodoventricular pathways being associated with the atrioventricular nodal fast pathway. Type I antiarrhythmic drugs, especially disopyramide and quinidine, were effective for the treatment of the re-entry tachycardia because of their depressive action on the nodoventricular pathway. Beta blockers were also effective because of their action on the atrioventricular nodal portion of the re-entry circuit in one patient and most probably due to atypical (atrioventricular nodal like) properties of a retrogradely conducting accessory pathway in a second patient.

One of the rare types of re-entrant paroxysmal tachycardia reflects the occurrence of re-entrance via nodoventricular fibres. In these unusual tachycardias anterograde conduction is usually via a right sided inserting nodoventricular pathway, producing a tachycardia resembling ventricular tachycardia with a left bundle branch block pattern.¹

Nodoventricular pathways might respond with an increase in refractoriness to drugs which depress the atrioventricular node or quinidine like agents, or both. There are few systemic data concerning the pharmacology of nodoventricular fibres and circus movement tachycardias using these fibres.

We report the drug responses, the electrophysiology of nodoventricular fibres as related to anterograde dual atrioventricular nodal pathways, and observations on the nature of retrograde conduction during nodoventricular circus movement tachycardia in three patients with re-entrant paroxysmal tachycardia.

Case 1

A 20 year old man with a five year history of paroxysmal tachycardia and no evidence of organic heart disease was studied. Electrocardiograms during sinus rhythm were normal (Fig. 1). During episodes of tachycardia the electrocardiogram showed wide QRS complexes (0.12 s) with left bundle branch block morphology, an axis of -20° , and a heart rate of 230 beats/min.

ELECTROPHYSIOLOGICAL STUDIES

Electrophysiological studies showed normal conduction intervals during sinus rhythm (AH: 70 msec, HV: 47 msec, QRS: 90 msec). With incremental atrial pacing from heart rates of 100 to 160 beats/min the AH interval gradually increased from 75 to 105 msec and concomitantly the HV interval gradually decreased from 30 to 10 msec with the appearance of partial pre-excitation. At atrial paced rates of 170 to 200 beats/min the His bundle electrogram merged into the QRS complex, which had a left bundle branch block appearance similar to his spontaneous tachycardia (Fig. 2). The time from stimulus to the onset of the QRS complex increased from 130 to 165 msec despite the shortening HV interval and appear-

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Fig. 1 Electrocardiograms of the three reported patients during sinus rhythm and during tachycardia.

ance of complete pre-excitation. The anterograde block rate for the anomalous pathway was 210 beats/min, with conduction continuing through the normal atrioventricular nodal pathway with a right bundle branch block aberration.

Atrial extrastimulus testing performed at three different cycle lengths showed dual atrioventricular nodal pathways. Accessory pathway beats were shown at the three atrial cycle lengths tested, the effective refractory periods being 410, 335, and 335 msec. The

accessory pathway beats occurred when the atrioventricular nodal fast pathway was used, and they had an effective refractory period longer than the effective refractory period of the atrioventricular nodal fast pathway.

Incremental ventricular pacing showed a normal retrograde sequence with a retrograde atrioventricular nodal block rate of 200 beats/min. From paced rates of 150 beats/min and faster a retrograde His deflection was clearly seen. Ventricular extrastimulus testing

Fig. 2 Case 1. Atrial pacing from the high right atrium (HRA) showing pre-excitation beats with left bundle branch block pattern during control study and after administration of propranolol and ouabain. Type I antiarrhythmics (procainamide, quinidine, disopyramide) resulted in loss of pre-excitation. PCS, proximal coronary sinus; HBE, His bundle electrogram; RVE, right ventricular electrogram; S, stimulus artefact.

Fig. 3 Study of nodoventricular re-entrant tachycardia using the single ventricular extrastimulus technique. Sustained tachycardia was induced before and after administration of propranolol and ouabain. Non-sustained tachycardia or single ventricular echoes were induced after type I antiarrhythmics. Abbreviations as in Fig. 2.

showed a single continuous retrograde curve with normal retrograde sequence. A retrograde His potential was always seen, and at close coupling intervals increases in VA paralleled increases in VH. An echo zone for antidromic re-entrant echo beats was defined.

Nodoventricular re-entrant tachycardia (Fig. 3) was readily induced with ventricular pacing or extra-stimulus. Spontaneous episodes were started by right ventricular premature contractions. The tachycardia was characterised by a left bundle branch block pattern (identical to the spontaneous arrhythmia and to the left bundle branch block pattern paced atrial beats). The cycle length of the tachycardia was 300 msec (heart rate of 200 beats/min). His potentials were clearly seen after the ventricular electrogram, most probably because of exclusive retrograde conduction through the left bundle branch His bundle (retrograde right bundle branch block). Endocardial ventricular activation mapping during tachycardia showed the proximal right ventricular outflow tract as the earliest site of ventricular activation. Retrograde atrial sequence mapping was normal with a ventriculoatrial conduction time of 125 msec.

PHARMACOLOGICAL STUDIES

After two control studies (on two separate days), which showed inducible sustained nodoventricular tachycardia (see above), serial drug testing was performed over several days (Fig. 2 and 3). Intravenous propranolol (0.1 mg/kg) had no effect on the anterograde anomalous pathway block rate and decreased the retrograde atrioventricular nodal block rate by 10 beats/min. Addition of ouabain (0.01 mg/kg) resulted in no change in the anterograde anomalous pathway block rate and a further 10 beats/min decrease in the retrograde atrioventricular nodal block rate. Re-entrant tachycardia was sustained with both drugs with an increase in the tachycardia cycle length of 20 msec.

After administration of procainamide 1.5 g intravenously the anomalous pathways were not seen during anterograde stimulation (increased refractoriness) and the retrograde block rate (atrioventricular nodal) decreased from 210 to 180 beats/min. Non-sustained re-entry tachycardia (maximum of three beats) was induced. A spontaneous sustained episode of tachycardia with a slight increase in cycle length was observed only at the end of the study while the procainamide concentration was decreasing (concentration of 6.1 mg%). Quinidine 1.6 g/day decreased the anterograde anomalous pathways block rate to below 160 beats/min and the retrograde atrioventricular nodal block rate to 170 beats/min. No tachycardia could be induced. Disopyramide 1.2 g/day had an identical effect to quinidine on the anomalous pathway anterograde block rate but decreased the retrograde atrioventricular nodal block rate to 140 beats/min. No tachycardia could be induced. Testing with the three type I antiarrhythmic drugs showed that induced non-sustained tachycardia or ventricular echoes always terminated with block in the anomalous

pathway (anterograde weak link). The patient has remained asymptomatic with quinidine for 10 months (previously having averaged one episode of tachycardia a month).

Case 2

A 44 year old woman with a five year history of recurrent palpitations and no evidence of organic heart disease was studied. Treatment at different times with digoxin, propranolol, or both, had had no effect on the incidence or duration of the palpitations. Treatment with quinidine and procainamide was started but had to be stopped promptly because of side effects. The resting electrocardiogram was normal (Fig. 1). A rhythm strip during an attack showed paroxysmal tachycardia (QRS complex of 0.08 s) at a rate of 250 beats/min and a paroxysm of non-sustained tachycardia (six beats) with wide QRS complexes. Twelve lead electrocardiograms of the tachycardia obtained during electrophysiological study showed a wide QRS complex tachycardia with left bundle branch block morphology and an axis of 60° (Fig. 1).

ELECTROPHYSIOLOGICAL STUDIES

Electrophysiological studies showed normal conduction intervals (AH: 66 msec, HV: 43 msec, QRS: 87 msec). Incremental atrial pacing from rates of 100 to 130 beats/min showed gradual increases in AH intervals from 70 to 100 msec. At paced rates of 130 to 190 beats/min, with the beginning of pacing and prolongation of the AH intervals, the HV interval shortened up to the point of merging inside the QRS complex. With the shortening of the HV interval the conducted beats had an incomplete left bundle branch block pattern and developed a complete left bundle branch block pattern when the His potential had completely merged inside the QRS complex. The time between the stimulus and the onset of the QRS complex increased from 170 to 190 msec despite the shortening of the HV interval and the appearance of complete pre-excitation. One to one conduction through the anomalous pathway was present up to paced atrial rates of 190 beats/min. At 200 beats/min Wenckebach periodicity with a narrow QRS complex was observed (anomalous pathway and atrioventricular nodal block rates). Atrial extrastimulus testing performed at driven cycle lengths of 500 and 400 msec showed dual atrioventricular nodal pathways with single atrioventricular nodal re-entrant atrial echoes (usual variety) and anomalous pathway conducted beats when a critical atrioventricular nodal conduction delay was achieved. The anomalous pathway effective refractory period was 300 to 250 msec (atrial limited) respectively. The anomalous pathway seemed to be functionally related to the atrioventricular nodal fast

pathway since fusion beats (between conduction through the His Purkinje system and anomalous pathway) were observed at the early portion of the curve while conduction occurred through the fast pathway. The atrioventricular nodal slow pathway (with single atrioventricular nodal re-entry atrial echoes) was observed only when conduction over the anomalous pathway failed.

Incremental ventricular pacing showed a normal retrograde sequence and a retrograde block rate of 200 beats/min. Ventricular extrastimulus testing showed a single retrograde conduction curve (with normal sequence). The H potential together with the retrograde A wave moved out of the ventricular electrogram when the ventricular extrastimulus was closely coupled. An echo zone for antidromic nodoventricular re-entrant ventricular echoes was also defined. Endocardial ventricular mapping was performed during atrial pacing with conduction through the anomalous pathway. The earliest site of activation could not be defined, but the anterior right ventricular areas (apex and anterior proximal outflow tract) were earlier than the posterior (inflow) areas.

Nodoventricular re-entrant tachycardia was readily induced with rapid ventricular pacing and occurred spontaneously after premature ventricular contractions. The tachycardia was characterised by a left bundle branch block pattern (identical to the one seen with atrial pacing). The cycle length of the tachycardia varied between 280 and 310 msec. The His potential was not visible. The retrograde atrial sequence was normal with a ventriculoatrial conduction time of 90 msec.

PHARMACOLOGICAL STUDY

After the control studies, which showed inducible sustained nodoventricular re-entry tachycardia, serial drug testing was performed over several days. Quinidine and procainamide were not tested because of previous intolerance.

Ouabain (0.01 mg/kg) resulted in no change in anterograde or retrograde block rates, nor in the anomalous pathway effective refractory period. Re-entry tachycardia was inducible and sustained with a cycle length similar to that in the control study. Intravenous propranolol (0.1 mg/kg) did not affect the anomalous pathway anterograde block rate or effective refractory period but decreased the retrograde block rate from 200 to 170 beats/min. Tachycardia could not be induced. Disopyramide (1.2 g/day) decreased both the anterograde anomalous pathway and retrograde atrioventricular nodal block rates from 200 to 150 beats/min, resulting in lack of induction of the tachycardia. No pre-excited beats were seen during atrial extrastimulus testing, implying a prolonged anomalous pathway effective refractory period. The

patient has remained asymptomatic on beta blockers for 12 months.

Case 3

A 17 year old girl with a history of myocardial contusion and recurrent tachycardia was studied. Treatment with digoxin and propranolol did not alter the frequency of palpitations. No evidence of organic heart disease was found. The resting electrocardiogram showed possible small delta waves (Fig. 1). The 12 lead electrocardiogram during tachycardia showed a wide QRS complex tachycardia at a rate of 250 beats/min with a left bundle branch block pattern and left axis deviation of -45° (Fig. 1).

ELECTROPHYSIOLOGICAL STUDIES

Electrophysiological studies showed a normal AH interval (70 msec) and variable HV interval with different degrees of pre-excitation. Incremental atrial pacing showed a gradual but slight prolongation of the AH and AV intervals. The AV nodal Wenckebach rate was 250 beats/min. At a paced rate of 240 beats/min, after the first conducted beat the successive conducted beats had a left bundle branch block pattern and a time between the stimulus and the onset of the QRS of 195 msec; they were not preceded by a His potential and were similar to the patient's spontaneous tachycardia. Atrial extrastimulus testing showed dual atrioventricular nodal pathways. At close coupling intervals on the atrioventricular nodal fast pathway, QRS conducted complexes had a left bundle branch block appearance, were not preceded by His potential, and showed a 20 msec increase in atrioventricular conduction time. When conduction jumped to the slow pathway the QRS complex became narrow. The effective refractory period of the left-bundle-branch-block-like conducted beats (anomalous pathway conducted beats) was 255 msec when tested at sinus rhythm (cycle length of 580 msec) and increased to 270 msec when tested at a driven atrial cycle length of 500 msec.

Ventricular pacing showed a retrograde block rate of 230 beats/min. The retrograde conduction sequence was abnormal with coronary sinus sites preceding right sided sites. Nodoventricular re-entrant tachycardia was readily induced with ventricular extrastimulus testing and rapid atrial and ventricular pacing. The tachycardia had a cycle length of 300 msec. It was characterised by wide QRS complexes with a left bundle branch block and left axis deviation pattern. No His potentials were seen during the tachycardia. Endocardial ventricular mapping of the tachycardia showed the inferior basal right ventricle as the earliest area of ventricular activation. Mapping of retrograde atrial activation showed the coronary

sinus as the earliest site (130 msec), followed by the proximal and mid-coronary sinus (135 and 140 msec respectively), the low septal right atrium (155 msec), and the high right atrium (180 msec).

PHARMACOLOGICAL STUDY

After control studies, which revealed inducible sustained nodoventricular re-entry tachycardia, serial drug testing was performed over several days.

Intravenous propranolol decreased the anterograde atrioventricular nodal block rate from 250 to 210 beats/min and decreased the anomalous pathway anterograde block rate from 240 to 200 beats/min. The retrograde block rate decreased from 230 to 180 beats/min. Re-entry tachycardia was not inducible. Intravenous procainamide (1 g over 20 min) was given during an episode of induced tachycardia. After seven minutes of infusion the tachycardia stopped spontaneously, with the site of block occurring in the anterograde limb (anomalous pathway). After completion of the procainamide infusion, repeat studies showed that procainamide did not alter the anterograde atrioventricular nodal block rate and that the retrograde block rate decreased to 190 beats/min. Anomalous pathway beats were not seen either during incremental atrial pacing or during atrial extrastimulus testing. With ventricular extrastimulus testing non-sustained nodoventricular tachycardia (10 beats) was induced, but subsequently sustained tachycardia was induced with an increase in cycle length from 300 to 320 msec. The procainamide concentration measured at that time was 6.8 mg/100 ml. Oral quinidine (1.6 g/day) and disopyramide (0.8 g/day) decreased the anterograde atrioventricular block rate to 190 beats/min, and no pre-excited beats were observed (total anomalous pathway block). The retrograde block rate decreased to 170 and 130 beats/min respectively. No tachycardia could be induced.

The patient was discharged and prescribed oral propranolol and has remained free of arrhythmias for two and a half years.

Discussion

Re-entry tachycardia due to nodoventricular fibres is relatively uncommon compared with the number of reported cases of the Wolff-Parkinson-White syndrome with re-entrant tachycardia. Nevertheless, there are enough reported cases to suggest certain characteristics of this type of fibre and of the re-entry tachycardia related to it.

Gallagher *et al.*¹ reported six patients with suspected nodoventricular pathways, all with re-entrant tachycardia. In addition, a review of the published work regarding this type of arrhythmia showed that

the resting electrocardiogram could be normal or show pre-excitation. QRS complexes during tachycardia showed a left bundle branch block pattern. This distinct electrocardiographic pattern suggested a right ventricular insertion of the nodoventricular fibre.

In most of the reported cases the re-entry circuit has been characterised by anterograde conduction over the accessory pathway (producing a wide QRS complex) and retrograde conduction over the His-Purkinje atrioventricular node axis.

In one of the cases of Gallagher *et al.* an inverse re-entry circuit was postulated. In other reports, the nodoventricular pathway has been considered as a bystander for the first beat of a re-entry circuit or for the entire length of the tachycardia with the atrioventricular node considered as the site of re-entry (atrioventricular nodal re-entry).²⁻⁴

Our patients presented with characteristics similar to those reported in previous cases. They were young and had no evidence of organic heart disease. They were referred for evaluation of rapid wide QRS complex tachycardia with ventricular tachycardia diagnosed in two of them. The basal electrocardiogram was normal in two patients, while a possible delta wave (with narrow QRS complex) was present in the other.

Electrophysiological studies showed normal basic conduction intervals in two patients while the third patient had variable HV intervals according to the degree of pre-excitation. Ventricular pre-excitation became clearly evident when atrial pacing or atrial extrastimulus testing induced enough (critical) atrioventricular nodal delay to allow greater ventricular depolarisation through the anomalous pathway. Two of our patients (cases 2 and 3) showed dual anterograde atrioventricular nodal pathways with conduction through the nodoventricular pathway related only to conduction via the atrioventricular nodal fast pathway. This contrasts with previous observations where the nodoventricular pathway was related to the atrioventricular nodal slow pathway.^{2,3,5} In case 1 conduction through the nodoventricular pathway was also related to the fast pathway, but as the refractory period of the accessory pathway was longer than the refractory period of the atrioventricular nodal fast pathway we cannot establish with certainty if the conduction was related only to the fast pathway. It is not clear in our patients why all three had dual atrioventricular nodal pathways and whether their occurrence relates to the occurrence of nodoventricular connections. It is also not clear why nodoventricular activation occurred only when the fast pathway was used and not when the slow pathway was used. The results imply an anatomical discontinuity within the atrioventricular node, with a nodoventricu-

lar pathway being in partial series at least with the atrioventricular nodal fast pathway and not the slow pathway. Since the anatomical locations of fast and slow atrioventricular nodal pathways are not known (if there is an anatomical basis for dual atrioventricular nodal pathways), it would only be speculative to try to explain this relation.

Reciprocating tachycardia was induced in all three patients. Ventricular stimulation (rapid pacing or extrastimulus) allowed the easiest induction of the tachycardia. The tachycardia had a left bundle branch block pattern in three patients; it had a 1:1 ventriculoatrial relation and conducted back to the atrium through the His-Purkinje atrioventricular node axis in two patients and was a concealed accessory pathway in the third patient.

The effect of antiarrhythmic agents on the properties of nodoventricular fibres and the associated re-entry tachycardia has not been closely examined. Different drugs such as digoxin, verapamil, quinidine, and disopyramide (in low doses) have been described as ineffective.⁶⁻⁸ Gallagher *et al.*¹ suggested that quinidine was effective in preventing tachycardia but they did not present any electrophysiological data in support of this.

In our patients disopyramide (0.8-1.2 g/day) was tested in all three patients, and proved to be the most effective drug, depressing both limbs of the re-entry circuit. Quinidine (1.6 g/day) seemed as effective as disopyramide for preventing tachycardia induction, but was tested in only two patients and its effects on the re-entry circuit were not as pronounced as disopyramide. Procainamide was ineffective in the two patients tested; the reason for this is unclear as procainamide shows similar type I antiarrhythmic actions to quinidine and disopyramide.

Ouabain was tested in only one patient and proved ineffective. Intravenous propranolol was effective in two patients, acting on the retrograde limb of the tachycardia. In one of the patients who responded to propranolol the retrograde limb of the re-entry circuit was the His-Purkinje-atrioventricular nodal axis while the second patient had an eccentric retrograde conduction, suggesting a retrogradely conducting anomalous pathway with atrioventricular node like properties.

The electrophysiological studies and drug responses in our patients provide some understanding of the properties of nodoventricular pathways. In two of the patients the nodoventricular pathways had electrophysiological and pharmacological properties similar to those observed in typical Kent bundles (decreased refractoriness with decreased cycle length, increased refractoriness after administration of type I antiarrhythmic drugs, and no change in refractoriness after administration of drugs that act on atrioventricu-

lar node like tissue—for example, ouabain and propranolol). In our last patient the nodoventricular pathway had some atrioventricular node like properties. Refractory periods increased with decreasing cycle lengths and propranolol decreased the block rate by 40 beats/min. Nevertheless, the effects of type I antiarrhythmic drugs were similar to the effects observed in the other two patients. The atrioventricular node like properties seen in the last patient could be related to properties of the anomalous pathway, presenting atrioventricular node like properties similar to some anomalous pathways of the Kent type or to properties of the atrioventricular nodal tissue adjacent to the emergence of the nodoventricular pathway from the atrioventricular node and not related to the nodoventricular pathway itself.

There is clearly a group of patients with relatively distinct characteristics including a tendency towards a normal electrocardiogram during sinus rhythm, paroxysmal tachycardia with a left bundle branch block pattern, and a capability for anterograde conduction with identical QRS complex pattern, when appropriate atrioventricular nodal delay and long anomalous pathway conduction times are achieved.

These patients can now be identified on clinical grounds. In addition, our electrophysiological studies showed appreciable sensitivity to at least some type I agents and sporadic sensitivity to atrioventricular node like depressant drugs for preventing paroxysmal tachycardia. These data should be useful to other doctors concerned with the management of patients with this unusual variety of paroxysmal tachycardia.

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