Disopyramide induced second and third degree atrioventricular block in patients with bifascicular block

An acute stress test to predict atrioventricular block progression

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SUMMARY Syncopal attacks in patients with bifascicular block may be due to both ventricular tachyarrhythmias and intermittent atrioventricular block in addition to non-cardiac causes and lead to antiarrhythmic treatment with drugs or pacemaker or both. The acute electrophysiological effect of intravenous disopyramide 2 mg/kg body weight given over five minutes on the His-Purkinje system was assessed in 27 patients with chronic bifascicular block undergoing evaluation for permanent pacemaker treatment. The predictive value of this pharmacological stress test as regards the development of atrioventricular block during follow up was analysed. The HV interval increased (mean 43%) and the QRS duration was prolonged (mean 24%). Intrahisian or infrahisian second or third degree atrioventricular block occurred in 14 patients after disopyramide administration, requiring temporary pacing in four of them. Before the electrophysiological study 15 of the 27 patients had had at least two syncopal attacks of suspected cardiac origin but no evidence of second or third degree atrioventricular block. Second or third degree atrioventricular block was subsequently recorded in five of these 15 patients during a mean of two years follow up. The sensitivity, specificity, and predictive value of second or third degree atrioventricular block produced by disopyramide administration including subsequent atrial pacing—a positive disopyramide test—as regards later development of atrioventricular block were 80%, 90%, and 80% respectively.

Intravenous administration of disopyramide to patients with bifascicular block and syncopal attacks of suspected cardiac origin may provoke atrioventricular block and asystole requiring immediate temporary pacing. Furthermore, a positive disopyramide test seems to have a significant value in predicting the later development of atrioventricular block.

Bifascicular block (left bundle branch block and right bundle branch block with left anterior or left posterior fascicular block) is associated with an appreciable risk of both ventricular tachyarrhythmias and second and third degree atrioventricular block.1-3 Disopyramide is a widely used antiarrhythmic drug with class I and class III properties (Vaughan Williams classification4) with a documented effect on ventricular arrhythmias.5 The safety of intravenous disopyramide infusion in patients with bundle branch block, including those with pronounced infranodal conduction delay, has been claimed.6 No other similar study has to our knowledge been published. Atrioventricular block progression has on the other hand been reported in one patient with bifascicular block given long term oral treatment with disopyramide.7

The purpose of this study was to investigate the short term effect and the potential value in predicting

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the development of atrioventricular block of disopyramide given during an invasive electrophysiological study of patients with permanent bifascicular block undergoing evaluation for implantation of a permanent pacemaker.

**Patients and methods**

**STUDY GROUP (TABLE 1)**

The study population consisted of 27 patients (24 men and three women; mean age of 68 (range 40-83; median 70) years) referred to our department for evaluation of the indications for permanent pacemaker treatment or admitted to our coronary care unit with a suspected acute myocardial infarction.

*Group 1*—Nine patients had documented second or third degree atrioventricular block, either during the acute phase of a myocardial infarction (four patients, cases 2, 6, 7, and 8), or during treatment with digitalis or a beta blocking drug (cases 1 and 9), or occurring spontaneously (cases 3, 4, and 5).

*Group 2*—Fifteen patients had chronic bifascicular block and at least two episodes of syncope of suspected cardiac origin. A complete history and physical examination supplemented by an electroencephalogram, orthostatic test, and other investigative procedures failed to explain the syncopal attack. Furthermore, at least 24 hours of electrocardiographic recording and exercise tests had not provided evidence of arrhythmias sufficient to explain the syncopal attacks—that is, no second or third degree atrioventricular block or advanced ventricular arrhythmias.

*Group 3*—Bifascicular block developed in three patients with an acute myocardial infarction. None of them had a history of syncope or previously documented second or third degree atrioventricular block.

The investigation protocol was approved by the
medical ethics committee of the hospital and the patients gave their informed consent.

DEFINITIONS
Bifascicular block is defined here as left bundle branch block or right bundle branch block with left axis deviation (-30° to -90°) indicating the presence of left anterior fascicular block, or right axis deviation (+110° to +180° degrees) indicating the presence of left posterior fascicular block. Terms and definitions relating to cardiac rhythm follow the recommendations by Hecht et al and Robles de Medina et al.

The electrophysiological study was performed with the patient fasting and unsedated, and treatment with cardioactive drugs was withheld for more than five half lives before the investigation. Three pacing leads with a distance of 1 cm between the electrodes were introduced percutaneously under local anaesthesia via a femoral vein. One quadripolar lead was positioned against the lateral wall, high in the right atrium for stimulation and recording. A tripolar lead was placed across the tricuspid valve for registration of the His bundle potential, and a bipolar lead was placed in the right ventricular apex for safety reasons. The intracardiac electrogram and at least surface leads I, II, and V1 were recorded on a Mingograph (Siemens-Elema, Sweden) with frequency limits of 50 and 700 Hz at a paper speed of 100 mm/s. Pacing was performed with a stimulus duration of 2 ms and a voltage of about three times the stimulation threshold using a stimulator for programmed pacing (Devices Ltd, England).

The HV interval was measured from the first rapid phase of the H wave to the earliest ventricular activity in any lead. The QRS duration was measured in lead II. The HV interval and QRS duration were given as the mean of at least three complexes rounded off to the nearest 5 ms. Atrial pacing was performed to determine sinus node recovery times, the atrial rate inducing Wenckebach block, and the atrioventricular nodal refractory period as previously described. Right ventricular pacing (see below) was performed at rates of 100 and 130 impulses per minute for periods of 10 and 30 seconds.

DISOPYRAMIDE TEST
Disopyramide (Roussel Laboratories Ltd, England) 2 mg per kg body weight (without upper dose limit) was given intravenously over five minutes. The duration of the HV and QRS intervals was measured within five minutes of the end of the infusion.

In this study a disopyramide test was considered to be positive in four circumstances. Firstly, the test was positive if second or third degree atrioventricular block appeared after disopyramide administration without any other interference of the spontaneous heart rate (pure pharmacological provocation). Secondly, the test was positive if second or third degree atrioventricular block, intraHis or infraHis, appeared during atrial pacing subsequent to the disopyramide administration. Thirdly, the test was positive if second or third degree atrioventricular block, infraHis or infraHis, appeared after abruptly terminated ventricular pacing subsequent to disopyramide administration. The reason for using right ventricular pacing as a stress test was the observation during the electrophysiological study of one of the first investigated patients (case 13). After disopyramide injection he developed complete infraHis heart block immediately after a spontaneous ventricular extrasystole and subsequently, and in a reproducible manner, after short periods of ventricular pacing. Finally, we also analysed the value of the HV prolongation induced by disopyramide administration. According to previous results the expected prolongation would be on average 20% after the same dosage. We arbitrarily chose a 50% prolongation as the lower limit for a potential predictor.

FOLLOW UP
During follow up the patients were seen three to four times a year, their history assessed, and a standard electrocardiogram recorded. When necessary the pulse generator was set low to elucidate the underlying spontaneous heart rhythm.

STATISTICAL METHODS
Mean values of electrophysiological variables, follow up duration, and number of available electrocardiographic recordings were given as arithmetic means or medians or both as indicated. Student's t test for paired observations was used for comparison of HV and QRS intervals before and after disopyramide administration. The predictive values of the different test variables in relation to the occurrence of second or third degree atrioventricular block were expressed as sensitivity, specificity, and predictive value of a positive test according to Galen and Gambino. Fisher’s exact test was used to test the result of the disopyramide test and the disopyramide test combined with an HV interval of ≥70 ms in the basal state in relation to the later development of second and third degree atrioventricular block.

Results
At the beginning of the electrophysiological study all patients had 1:1 conducted sinus rhythm except one (case 5), who had second degree atrioventricular block.

The His-Purkinje conduction time was significantly prolonged, with a mean increase of the HV interval of
Disopyramide induced second and third degree atrioventricular block

43% (p < 0.001). Two distinct His potentials were recorded in five patients: the H1H2 interval increased in three (case 2: 90 ms, case 15: 35 ms, case 24: 10 ms), did not change in one (case 6), and could not be measured in one (case 3) because of complete heart block. In 10 patients the HV prolongation produced by disopyramide was 50% or more (Table 1). The QRS duration was prolonged by a mean of 24% (p < 0.001).

SECOND AND THIRD DEGREE
ATRIOVENTRICULAR BLOCK AFTER
DISOPYRAMIDE (TABLE 1)
The disopyramide administration induced intrahisian or intrahisian second (cases 1, 2, 7, 9, 14, 15, 16, 17, 18, and 21) or third (cases 3, 5, 13, and 20) degree atrioventricular block in a total of 14 patients. There was no significant difference in types of bifascicular block.

Group 1—Of the nine patients, six (67%) developed atrioventricular block after disopyramide injection, three from pure pharmacological provocation, two from subsequent atrial pacing, and one after ventricular pacing. Of the other three patients, two had had a myocardial infarction. One patient (case 6) had an anterolateral wall infarction two weeks before the investigation and complete heart block after verapamil treatment for rapid atrial fibrillation. The other patient (case 8) had an infarction of the inferior wall, with involvement of the anterior and lateral parts of the left ventricular wall one month before the study.

Group 2—Disopyramide induced atrioventricular block by pure pharmacological provocation in three patients, by atrial pacing in two (plus one of the previous three), and after ventricular pacing in three (plus one of the two resulting only after atrial pacing).

Group 3—Disopyramide did not induce any atrioventricular block.

In four (cases 5, 7, 13, and 20) of the 14 patients with disopyramide induced second and third degree atrioventricular block, prolonged asystole or haemodynamically inadequate heart rate required temporary ventricular pacing. Adequate spontaneous heart rate resumed within less than one hour. Two of these four patients had no evidence of myocardial or valvar disease. A transient episode of hypotension occurred in one patient (case 7). No other adverse effects were observed.

FOLLOW UP
The patients were followed for a mean of 24 months, during which time eight died, all but one from cardiovascular causes. Ventricular fibrillation occurred in one case of hospital death (case 6). Syncopal attacks during follow up occurred in three patients, one of whom died of an acute myocardial infarction and the others of a stroke.

The patients were seen a mean of 11 times and an electrocardiogram recorded 2–25 times (median 12 available recordings).

Second or third degree atrioventricular block was recorded in two of the nine patients in group 1 during follow up. In five (four of 11 with right bundle branch block with left anterior fascicular block and one of two with left bundle branch block) of the 15 patients in group 2 second or third degree atrioventricular block occurred 3–38 months after the electrophysiological study. In none of the three patients in group 3 was second or third degree atrioventricular block recorded during follow up.

PREDICTION OF ATRIOVENTRICULAR BLOCK
PROGRESSION (TABLE 2)
The results of possible prognostic variables and tests—that is, the presence of an HV prolongation to >70 ms in the basal state and a positive disopyramide test—were related to the occurrence of second or third degree atrioventricular block.

An HV interval of >70 ms in the basal state was seen in five patients, two in group 1 and three in group 2. This finding was a specific (90–92%) but insensitive (29–40%) indicator of previous or subsequent occurrence of atrioventricular block.

The results of the disopyramide test are given separately for the three groups. In this analysis the three different groups served different purposes. Group 1 gave an indication of the sensitivity and group 3 of the specificity of the disopyramide test. Group 2 was then used to define the prognostic or predictive values.

In group 1 a comparison was made with the episodes of atrioventricular block that were recorded before the electrophysiological study. As by definition all these patients had had transient second or third degree atrioventricular block this comparison gave an indication of the sensitivity of the disopyramide provocation. Seven out of nine patients had a positive test, which gave a sensitivity of 78%.

Group 3 on the other hand indicated the specificity of the disopyramide provocation as the patients had neither a history nor symptoms of second or third degree atrioventricular block. One of these three patients had an HV prolongation of more than 50% after disopyramide; otherwise the disopyramide test was negative. Atrioventricular block was not recorded in these patients during 12, 50, and 53 months of follow up.

Group 2 comprised patients in whom a test like the disopyramide provocation would probably have its clinical applicability in the future—that is, as a prognostic test. Initially, the disopyramide test was tentatively considered to be positive in four circumstances.
Table 2  Prognostic value of different physiological variables and tests in determining previous (group 1) and subsequent (group 2) evidence of second/third degree atrioventricular block

<table>
<thead>
<tr>
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<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Predictive value (%) of positive test</th>
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<td>Groups 1, 2, and 3</td>
<td>Groups 1, 2, and 3</td>
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<td>HV interval ≥70 ms (basal state)</td>
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<td>Disopyramide test (DT) and:</td>
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<td>PPP and atrial pacing (AP)</td>
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<td>90</td>
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<tr>
<td>Change in HV interval ≥50%</td>
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<td>50</td>
<td>40</td>
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<tr>
<td>DT, PPP/ AP, or HV ≥70 ms (basal state) or all</td>
<td>100</td>
<td>90</td>
<td>83</td>
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*p = 0.017; **p = 0.002 (Fisher’s exact one tailed test).

Table 2 shows that the result of ventricular pacing and an HV prolongation of ≥50% after disopyramide injection both had poor sensitivity and specificity for the occurrence of second or third degree atrioventricular block. If, however, a positive disopyramide test was defined as second or third degree atrioventricular block occurring with pure pharmacological provocation and after subsequent atrial pacing the prognostic value of the test is greatly improved—namely sensitivity 80%, specificity 90%, and predictive value of a positive test 80%.

The best predictive value was, however, obtained if an HV prolongation to ≥70 ms in the basal state and a positive disopyramide test were combined. In our group of patients this latter combination gave a sensitivity of 100%, a specificity of 90%, and a predictive value of a positive test of 83%.

Discussion

SHORT TERM EFFECT OF DISOPYRAMIDE

Contrary to previous experience, we thus found that the intravenous administration of disopyramide 2 mg/kg body weight can induce second and third degree atrioventricular block in patients with bifascicular block. In the study by Desai et al patients with a recent acute myocardial infarction and patients with evidence of second or third degree atrioventricular block were excluded. Sixteen of their 22 patients had bifascicular block and six right bundle branch block. The disopyramide dose was the same, but the infusion rate was seven minutes in their study and five minutes in ours, the difference probably being of little importance. A point of utmost importance is the presence of cardiogenic syncopal attacks, which could either be attributed to ventricular tachyarrhythmias or intermittent second or third degree atrioventricular block. In the report by Desai et al the presence or absence of syncopal attacks was not stated. Assuming that none of their patients had had syncopal attacks, their group of patients would be comparable to our group 3, and then no discrepancy in results would exist. It is, however, the patients with syncopal attacks who require most diagnostic and therapeutic consideration.

In two recent reports of patients with bifascicular block and syncope of uncertain origin the ability of subsequently performed programmed stimulation to induce ventricular tachycardias has been taken as evidence for their causative role. Our study protocol did not include programmed stimulation for the routine provocation of ventricular tachyarrhythmias, but it was performed in one patient (case 19). In this patient, non-sustained ventricular tachycardias could be induced in the right ventricular outflow tract before, but not after, disopyramide administration. As the disopyramide was well tolerated and the electrophysiological study was otherwise normal, this patient was subsequently prescribed oral disopyramide. He has been free of symptoms during follow up. As regards the other patients, the absence of recurrent syncopal attacks in most cases indicated the absence also of ventricular tachycardias, although it cannot be excluded that this arrhythmia was the cause of the previous syncopal attacks and that spontaneous remission had occurred.

ATRIOVENTRICULAR BLOCK PROGRESSION IN PATIENTS WITH BIFASCULAR BLOCK

The prevalence of bifascicular block is 1–1.5% in the adult population, but the yearly incidence of atrioventricular block progression is only 1–4%. No clinical or standard electrocardiographic features have been found to predict progress to second or third degree atrioventricular block.

Three principally different electrophysiological factors of prognostic value have previously been identified: (a) an HV prolongation in the basal state, (b) second or third degree atrioventricular
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block in the His-Purkinje system during atrial pacing,12 and (c) pharmacological provocation of atrioventricular block with procainamide20 and ajmaline.21

The reason for choosing disopyramide in this study was that it has both class I antiarrhythmic properties, like procainamide and ajmaline, and also class III properties and anticholinergic effects.4 Our hypothesis was that latent His-Purkinje disturbances could be provoked (a) by the class I and III antiarrhythmic effects and (b) by atrially paced impulses reaching the distal conduction system at higher rates as vagally depressed atrioventricular nodal conduction would be unmasked by the anticholinergic effect. Disopyramide would thus provide an opportunity to combine the principles (b) and (c) in the previous paragraph.

The occurrence of second and third degree intrahisian or infrahisian atrioventricular block during disopyramide administration may be a provocation of intermittent atrioventricular block, an unmasking of a latent predisposition for atrioventricular block, or an adverse reaction to the drug that is unrelated to prognosis. The critical factor for evaluating the prognostic importance of such a reaction is of course the outcome during follow up. The patients were followed with repeated standard electrocardiographic recordings. This method has, however, obvious limitations in evaluating prognostic tests for the development of atrioventricular block. Jensen et al found that more than 50% of patients with third degree atrioventricular block and syncopal attacks had intermittent atrioventricular block and about 75% of the patients in the group with intermittent atrioventricular block had bifascicular block during sinus rhythm.22 It is therefore possible that we were not able to detect intermittent atrioventricular block in some patients. But even with this reservation, we found the disopyramide test to be of potential value in predicting atrioventricular block progression (Table 2). In our limited group of patients the predictive value of the disopyramide test clearly exceeded the values reported concerning other predictors such as HV prolongation in the basal state,13-3 infrahisian or infrahisian atrioventricular block during atrial pacing,12 which did not occur in any of our patients, and the value of the ajmaline test.21 The validity of the results of the disopyramide test must, however be evaluated in a prospective study of a larger group of patients. The use of a bradycardia indicating pacemaker23,24 would then offer a safe and sensitive method for detecting clinically significant permanent or intermittent bradycardias due to atrioventricular block.

If we analyse the results in the group of patients with a previous acute myocardial infarction the disopyramide test seems to have a limited value. The number of patients is, however, small, and the interval between the infarction and the electrophysiological study differs. Two patients (cases 2 and 7) with a false positive disopyramide test as regards later atrioventricular block development were studied three weeks and one month after the infarction, which may be too early.

ADVERSE EFFECTS
An adverse effect of disopyramide administration was seen in one patient. He had before the study had a massive anterior myocardial infarction and was mobilised but not haemodynamically entirely stabilised. This patient was one of the four who required temporary pacing. The pronounced but transient fall in blood pressure was probably due to a combination of inadequate heart rate and impaired ventricular performance which was further depressed by the negative inotropic effect of disopyramide.25

CONCLUSION
The acute intravenous administration of disopyramide to patients with bifascicular block may induce second and third degree atrioventricular block both in patients with previously documented transient second or third degree atrioventricular block and in patients with a history of syncope of suspected cardiac origin. Furthermore, this procedure can be used as a stress test of the His-Purkinje conduction system in the latter group of patients and seems to have a potential value in predicting subsequent development of second or third degree AV block.

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