High-degree atrioventricular block during anti-arrhythmic drug treatment: use of a pacemaker with a bradycardia-detection algorithm to study the time course after drug withdrawal

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Aim This study examines the recurrence of high-degree atrioventricular block (AVB) during a follow-up period of 2 years in patients with restored AV node function after antiarrhythmic drug withdrawal at implantation of a pacemaker.

Methods Nine men and eight women (77 ± 7 years) taking antiarrhythmic drugs (beta-receptor blockers in 15) and presenting with high-degree AVB were followed for 2 years after being taken off drugs upon receiving a permanent pacemaker with special bradycardia detection software.

Results At inclusion, surface ECG identified two subsets of patients: a QRS duration ≤120 ms (n = 5) and those with a QRS duration >120 ms (n = 12). During the 2-year follow-up, progression to high-degree AVB occurred in these groups: 1/5 (20%) and 9/12 (75%) P, 0.05. Six patients had to be restarted on drugs, mostly beta-receptor blockers, due to atrial tachyarrhythmias: 3/5 and 3/12. In total, 16 patients (94%) either developed high-degree AVB needing pacing or atrial tachyarrhythmias requiring drug treatment.

Conclusion Patients on beta-receptor blocking drugs and QRS width >120 ms developing high-degree AVB should be recommended a pacemaker without further investigation or observation.

KEYWORDS
Atrioventricular block; Drugs; Pacemaker; Pacemaker algorithm

Introduction
According to current guidelines, patients with symptomatic bradyarrhythmias due to high-degree atrioventricular block (AVB) have a class I indication for pacemaker implantation.1 The reason for pacemaker treatment is not only the improvement in bradycardia-related symptoms but also the survival benefit of this therapy.2 If the AVB is drug induced and the condition is expected to resolve and/or unlikely to recur, pacemaker implantation is generally contraindicated.1 In guidelines for treatment of bradyarrhythmias in the elderly, withdrawal of drugs is recommended as the first approach to management.3 In a review article,4 the authors recommended permanent pacing in this clinical setting, but this recommendation was based on a study of selected patients with bifascicular block only.5

A search in the database of Medline for drug-induced AVB revealed some case reports on digoxin, calcium channel blockers, and beta-blockers as potential causes of AVB, that resolved in some cases after withdrawal of the drug, but there were also patients who received a pacemaker despite drug withdrawal. No systematic studies were found. In the clinical setting of bifascicular block and syncope, class I A antiarrhythmic drugs can be used for investigational purpose to provoke a latent defect in the His-Purkinje system. There are systematic studies of class I antiarrhythmic drugs such as ajmaline, procainamide, and disopyramide,5 but not for other antiarrhythmic compounds from classes 2, 3, and 4 as provocation substances that induce AVB.

The present study was conducted because of the lack of clear recommendations in the management of patients on antiarrhythmic agents who develop AVB and the role of antiarrhythmic agents in development of bradyarrhythmias. The aim was to investigate whether withdrawal of antiarrhythmic drugs had a permanent reversal effect on the AVB.

Methods
Patient population
All patients admitted with both symptomatic high-degree AVB and treatment with an antiarrhythmic drug were given a
permanent pacemaker. Patients were included in our study if the antiarrhythmic drug could be withdrawn and if the AVB disappeared during the hospital period or during the time to the first follow-up at 1 month. The decision to withdraw the antiarrhythmic drug was made by the physician in charge, depending on the indication for drug therapy and the clinical situation. The disappearance of AVB during hospitalization was registered on continuous ECG monitoring or by pacemaker data at the first follow-up visit. During the inclusion period, all patients living in the southern part of Stockholm were referred to Karolinska University Hospital at Huddinge for pacemaker implantation. The definition of an antiarrhythmic compound was a drug of Vaughan Williams classes I–IV and digitalis. Exclusion criteria were heart valve surgery during the last year and permanent atrial fibrillation.

Pacemaker system
All patients received a Chorus RM (7034) DDD-R pacemaker (Ela Medical, Le Lessis Robinson, France). An algorithm for pause and bradycardia analysis was loaded temporarily (during the study period) into the RAM memory of the pacemaker. The pacemaker mode was VDI. Upon detection of bradycardia, atrial, and ventricular marker channels were saved to allow retrospective evaluation. The lower rate of the pacemaker was set to 50. The ventricular pause rate was programmed to 30 bpm for three consecutive paced beats. A pause was diagnosed and saved with a marker. The pacing cycle was then decreased by 63 ms from cycle to cycle until the programmed lower rate was reached. The detection of pauses was inhibited for 50 cycles after lower rate pacing (50 bpm) had been reached after a pause. Up to three episodes of pauses were allowed until the pause function was stopped. An intermediate bradycardia zone between a surveillance rate of 40 and the pause rate of 30 bpm was programmed for safety reasons. To fulfill these criteria, a period of 20 beats had to be sensed below the surveillance rate before a marker for bradycardia was saved. The time and date of the pauses and bradycardia events were stored in the memory of the pacemaker. This algorithm has been described and used in other studies.6,7

Follow-up and endpoint
Whether the AVB resolved during initial hospitalization or during the first month post-implant, the pause and bradycardia detection algorithm was programmed into the RAM memory of the pacemaker. These patients were then followed every 6 months for 2 years. The primary endpoint was to evaluate the recurrence of AVB. A secondary endpoint was to register other brady- or tachy-arrhythmias during the study period.

In case of detection of a bradycardia episode, the pacemaker was reprogrammed to standard VVIR or DDDR mode and the bradycardia algorithm was inactivated.

Categorical data were compared using the χ² test. The Kaplan-Meier method was used to estimate the AVB free interval during the follow-up.

The medical ethics committee approved this study, and the patients gave their consent after receiving appropriate information.

Results
During the inclusion period of 2 years, 585 new permanent pacemaker systems were implanted at our clinic. Seventeen patients were included in the study with a mean age of 77 ± 7 years. Eight patients were women (47%). The clinical characteristics of the study population are listed in Table 1. The majority of patients had a history of syncope at presentation (n = 13; 76%). On admission one patient had a stable 2:1 second-degree AVB. Eight patients had intermittent second- or third-degree AVB with one to several symptomatic attacks per day. Eight patients had constant third-degree AVB and four were haemodynamically compromised necessitating isoprenaline or temporary pacing. In patients in whom AVB resolved, a 12-lead surface ECG most often showed left bundle branch block (n = 7; 41%). In one patient, ECG showed signs of intraventricular conduction disorder in terms of prolonged QRS duration >120 ms, but the classification into a type of bundle branch block was not possible. The mean QRS duration was 130 ± 32 ms. Medications affecting the conduction system before entry to the study are summarized in Table 1. The mean time for medical treatment before admission was 15.5 months (range 0.5–28) and the time from initiation of the drug to the first symptom suggestive of an arrhythmia was 4.7 months (range 0.5–18), Table 1.

Fifteen patients (88%) were treated with beta-receptor blockers at the time of admission to the hospital. Sotalol, verapamil, and digoxin were also present alone or in combination in three patients (Table 1). The indications for treatment with these agents were hypertension (n = 8), ischaemic heart disease (n = 6), heart failure (n = 3), essential tremor (n = 1), and suspected but not documented paroxysmal atrial fibrillation (n = 1). Echocardiography was performed in all patients and showed a mean ejection fraction of 56 ± 12%.

Figure 1 shows all events and results for each patient from admission to the end of the 2-year follow-up, except for patient 7. This patient died of pulmonary carcinoma after 15 months. At the 12-month visit, the pacemaker had not detected any episode of pause or bradycardia. Thirteen patients had a pause detected. The marker channel diagnosed high-degree AVB in 10 of these patients and the pacemaker was reprogrammed from VDI to DDDR mode. In three patients (2, 14, 16) the algorithm diagnosed sinus pauses with a duration of 5, 30, and 4 s, respectively (Figure 1). In patient 16, one bradycardia event was recorded that ended with a pacing sequence of 50 bpm. In all three events showing a sinus pause, sinus bradycardia was detected for some seconds with a rate below 40 bpm preceding the pause. No patients experienced any pause-related symptoms due to the algorithm during the study period.

The mean time from inclusion to documented high-degree AVB was 9 ± 7 months. Figure 2 shows freedom from high-degree AVB as a function of time and without antiarrhythmic drugs.

Six patients (1, 3, 6, 8, 9, 11; 35%) with the pacemaker in a bradycardia-detecting mode developed symptomatic atrial fibrillation or atrial flutter during the follow-up. None of these patients had a history or documented symptomatic tachyarrhythmia. For rate regulation and arrhythmia termination, they all received sotalol (except patient 1 who was treated with metoprolol). Three of these six patients (3, 6, and 11) were hospitalized due to atrial fibrillation and symptomatic high rate. Sotalol treatment was initiated. After 2, 4, and 6 days high-degree AVB recurred. These patients were reprogrammed from VDI to DDDR/VVIR mode.

After reprogramming the pacemaker the number of mode-switches was identified. Four of ten patients (40%) who were not taking antiarrhythmic drugs with the pacemaker in DDDR mode had one or more mode-switch
<table>
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<tr>
<th>Patient no.</th>
<th>Age</th>
<th>Sex</th>
<th>Rhythm on admission</th>
<th>QRS-morphology</th>
<th>QRS-duration</th>
<th>EF (%)</th>
<th>Indication for treatment</th>
<th>Dose</th>
<th>Drug</th>
<th>Duration of medication (months)</th>
<th>Time to symptoms (months)</th>
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<td>RBBB + LAFB</td>
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<td>200</td>
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<td>Heart failure</td>
<td>5</td>
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<td>AV II, M 2</td>
<td>LBBB</td>
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<td>60</td>
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<td>100</td>
<td>Metoprolol</td>
<td>10</td>
<td>2</td>
<td>Several syncopes</td>
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</table>

AF, atrial fibrillation; AV, atrioventricular block; hg, high grade; Incl, inclusion; IVCD: intraventricular conduction delay; IHD, ischaemic heart disease; LBBB: left bundle branch block; M 2, Mobitz type 2; RBBB: right bundle branch block; LAFB: left anterior fascicle block.

*QRS-morphology during AV conduction.
Bradycardia-detection algorithm and drug-induced AV block

In combination with the algorithm—AIDA—these events were interpreted as paroxysmal atrial tachyarrhythmias. Two subgroups of patients were identified based on the 12-lead ECG at inclusion: patients with normal QRS complexes (five patients) and those with a broad QRS (≥120 ms) morphology. This latter group included patients with right bundle branch block (two), intraventricular conduction delay (one), and bifascicular block (nine) (Table 1). During the 2-year follow-up, progression to high-degree AVB occurred in these subgroups in the following distribution: 1/5 (20%) and 9/12 (75%) patients \( P < 0.05 \). The corresponding figures in those six patients who started on antiarrhythmic drugs due to atrial tachyarrhythmias and high-ventricular rate were 3/5 and 3/12 patients, respectively. In total, 16 patients (94%) developed either high-degree AVB needing permanent pacing or atrial tachyarrhythmias requiring antiarrhythmic drug treatment and subsequent pacemaker treatment.

**Discussion**

We observed that beta-blockers were the most common antiarrhythmic drug involved in development of transient AVB. After drug withdrawal and during a follow-up period of 2 years, 9 of 12 patients with impaired intraventricular
limited effects on the healthy cardiac conduction system,8 treatment of neurological and psychiatric disorders has channel blocker, carbamazepine, frequently used in the impairment of the cardiac conduction system. A sodium 2 years.9

symptoms disappeared. Carbamazepine-induced malfunc-
tion did not predict pacemaker dependency in the following
tion in the atrioventricular node or intraventricular conduc-
tion (QRS \( \geq \) 120 ms) developed AVB. Six patients developed symptomatic atrial tachyarrhythmias that necessitated reintiation of antiarrhythmic drug therapy.

A possible hypothesis was that antiarrhythmic drugs act on a susceptible or a vulnerable conduction system, a condition that is often found in the elderly7 and cause transient impairment of the cardiac conduction system. A sodium channel blocker, carbamazepine, frequently used in the treatment of neurological and psychiatric disorders has limited effects on the healthy cardiac conduction system,8 but it has a more pronounced effect in patients with cardiac conduction disorders, causing impaired atrioventricular or intraventricular conduction.7 Most of the patients considered for this study had taken carbamazepine for several months or years and suddenly developed symptoms, mostly syncope. After withdrawal of the drug, the cardiac symptoms disappeared. Carbamazepine-induced malfunction in the atrioventricular node or intraventricular conduction did not predict pacemaker dependency in the following 2 years.9

In a large retrospective study of 8770 patients >65 years with a history of atrial fibrillation and myocardial infarction, only digoxin and amiodarone but not beta-blockers were associated with an increased risk of pacemaker implantation. There was no information of QRS duration in this study.10

Based on the 12-lead ECG, 12 patients had bundle branch block. However, a 12-lead surface ECG is insufficient to determine if the His–Purkinje system is normal. In asymptomatic patients or in the presence of syncope and bifascicular block, a baseline electrophysiological study with pharmacological provocation by a class I antiarrhythmic drug is warranted for evaluation of the His–Purkinje system and future pacemaker dependence.5,11,12 Brignole et al. studied a population with a negative electrophysiological study with an implanted loop recorder and found AVB in 17/52 patients (33%) after a 3 to 15-month follow-up.13 Bergfeldt et al. studied patients with syncope and bifascicular block or transient AVB (n = 11) with repeated ECGs. Some patients were followed with a bradycardia-detecting pacemaker. High-degree AVB developed in 16/37 (43%) patients after a mean of 63 months.14 In the current study, nine patients had bifascicular block and a transient high-degree AVB. Sufficient scientific data exist to recommend a pacemaker in this group of patients. Further investigation with an invasive electrophysiological study is recommended in the group of patients with normal intraventricular conduction on a 12-lead ECG, since only 1/5 of the patients became pacemaker dependent in the present study during the follow-up.

The concept of a bradycardia-detecting algorithm, which can be downloaded into the pacemaker after implantation, opens up the possibility to increase our knowledge about the time course of bradyarrhythmias. Previous studies with bradycardia-detecting algorithms have shown a good relationship between pacemaker detected bradycardia and progression to high-degree AVB with only one ventricular lead.14,15 However, dual-chamber bradycardia-detecting pacemakers indicate that sinus arrest is also a common phenomenon in patients with suspected AVB.7,16 A phenomenon also found in this study (Figure 1). The same algorithm used in the present study has been used in a study of unexplained syncope to confirm a suspected mechanism of bradyarrhythmias, a technique that produced a good diagnostic yield.16 There is a need for this software to be temporarily programmed into a pacemaker for evaluation of unexplained syncope where a pacemaker in some clinical settings is more appropriate to implant than a loop recorder. The Sorin Group have developed the AAISafeR2 and Medtronic the MVP algorithms for pacemakers during the last year. These algorithms are designed to promote atrial conducted rhythm and to minimize ventricular pacing, but can be used for studies similar to the present one with some limitations.

Limitations of the study
The present study consisted mostly of patients with bifascicular block. In this subgroup, there are several studies that support implantation of a permanent pacemaker.5,13 Our intention was to include more patients into the other subgroup, but unfortunately the study had to be terminated because the pacemaker model chosen became unavailable and no other model allowed us to download the pause and bradycardia algorithm. Three patients 8, 11, and 12 had normal AV node conduction at discharge, but were included in the study first at the 1-month follow-up. The reason to this delay was the absence of persons on duty with the knowledge and permission to perform the downloading of software into the pacemaker.

Conclusion
In the present study, including patients with symptomatic high-degree AVB during predominantly beta-receptor drug treatment in whom AVB resumed after drug withdrawal. Two subgroups of patients were identified based on the 12-lead ECG at inclusion: patients with a QRS duration <120 ms and those with a QRS \( \geq \) 120 ms. During the follow-up, progression to high-degree AVB was significantly
greater in those patients with pre-existing QRS prolongation, mostly due to bundle branch block compared with those patients with a normal QRS duration. It is clear from this study that patients with pre-existing bundle branch block who, during administration of beta-receptor blocking drugs, develop high-degree AVB should be recommended a pacemaker without further investigation or observation. On the other hand, in the small group of patients with normal QRS duration, it is advisable to recommend an electrophysiological study before making a decision about pacemaker implantation, since only one patient developed high-degree AVB during the follow-up.

Acknowledgements

The authors thank the staff at CardioNord, the local Ela representatives in Sweden at that time for their competent assistance.

References