The RR index test for the differentiation of atroioventricular nodal block from His–Purkinje block during incremental atrial pacing in patients with bifascicular block

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Aims
His–Purkinje block induced by incremental atrial pacing is highly predictive of an impending high degree atroioventricular block in patients with bifascicular block. The His potential is, however, sometimes not measurable or is lost in the ventricular depolarization. The aim of this study was to evaluate whether the comparison of RR intervals before and after atroioventricular block, induced by incremental atrial pacing, could differentiate between atroioventricular nodal and His–Purkinje block in patients with bifascicular block.

Methods and results
In 98 patients with bifascicular block, incremental atrial pacing was performed as part of an invasive electrophysiological study. An ‘RR index’ was constructed by calculating the numerical difference between the RR interval immediately before and after the atroioventricular block divided by the RR interval immediately before the pacing-induced block. Endocavitary recording of the His bundle potential was used for defining the level of atroioventricular block. The median RR index was 0.98 (range 0.88–1.02) in recordings with His–Purkinje block and 0.49 (range 0.11–0.89) in recordings with atroioventricular nodal block (P<0.001). An RR index of ≥0.85 had a sensitivity of 100% and a specificity of 99% for the identification of atroioventricular block localized to the His–Purkinje system.

Conclusion
The use of an RR index is a helpful tool in the differentiation of His–Purkinje from atroioventricular nodal block in patients with bifascicular block undergoing incremental atrial pacing as part of an invasive electrophysiological study.

Key Words: Bifascicular block, high-degree atroioventricular block, electrophysiological study.

Introduction
Patients with bifascicular block (left bundle branch block or right bundle branch block with left anterior or posterior fascicular block) have an increased risk for the development of high-degree atroioventricular block[1–3]. No non-invasive test is useful in predicting this arrhythmia, but an invasive electrophysiological study, during which the His potential is recorded, has been found to be of prognostic value[1–3,9]. The stimulation protocol often includes incremental atrial pacing which usually results in atroioventricular nodal block (block proximal to the His). A block within or below the His bundle, both when performed in the basal state[6] and after pharmacological provocation[7,8], suggests conduction abnormality in the His–Purkinje system and has been found to be highly predictive of a subsequent high-degree atroioventricular block. The His bundle potential is, however, sometimes not measurable or is hidden within the ventricular depolarization during incremental atrial pacing, making it impossible to define the level of block. A test which can differentiate between atroioventricular nodal and His–Purkinje block without the need for His potential recording would therefore be helpful.

The aim of this study was to evaluate whether the comparison of RR intervals before and after atroioventricular block induced by incremental atrial pacing, could differentiate between atroioventricular nodal and His–Purkinje block in patients with bifascicular block.

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Methods

This investigation was performed as part of a larger project studying the substrate for brady- and tachyarrhythmias in patients with bifascicular block.\(^9\)\(^10\)

Patients

An invasive electrophysiological study was performed in 98 patients with chronic bifascicular block, defined as left bundle branch block (n = 54) or right bundle branch block together with left anterior (n = 41) or left posterior fascicular block (n = 3). Forty patients had a history of syncope which remained unexplained after a 24 h ambulatory ECG recording and after a symptom-limited exercise test. Seventy-seven patients were men and the mean age ± SD was 67 ± 12 years. All patients were in sinus rhythm.

Electrophysical study

This was performed in the post-absorptive, unsedated state after the withdrawal of all antiarrhythmic medication for ≥5 elimination half-lives. Three quadripolar catheters were positioned, via the femoral vein, in the high right atrium, in the His bundle position and in the right ventricular apex. Atrioventricular nodal function was assessed in all patients at baseline by the mean AH interval from three consecutive beats and the effective refractory period of the atrioventricular node (atrioventricular-node-effective refractory period) by coupling an increasingly premature stimulus to a train of 8 beats at a basic rate of 100 beats . min \(^{-1}\) (the S1S2 technique). Atrioventricular block was induced in all patients by incremental atrial pacing with the reduction of pacing cycle length by 10 ms every second beat until atrioventricular block was reached. Stimuli were delivered at twice the diastolic threshold with a pulse width of 2 ms.

In order to increase the sensitivity of the electrophysiological study, 72 patients with an ejection fraction >35% were given disopyramide intravenously, 2 mg per kg body weight with a maximum dose of 150 mg, over a period of 5 min\(^7\). Of the 26 patients with an ejection fraction ≤35%, 12 patients with a pacing-induced atrioventricular block at stimulation rate less than 120 beats . min \(^{-1}\) were given atropine, 0.02 mg per kg body weight, over a period of 30 s. The stimulation protocol was then repeated. Incremental atrial pacing was performed twice in the basal state and after disopyramide or atropine administration unless atrial fibrillation was induced or if the patient had severe discomfort due to high stimulation rates.

A 10-channel Siemens-Elema Mingograph was used for electrocardiographic recording and included intracardiac registration from the atrium, proximal, middle and distal portions of the His bundle and from the right ventricular apex as well as surface ECG leads V\(_1\), V\(_6\), I and II. The AH interval was measured from the onset of atrial deflection to the earliest His bundle deflection in any of the His bundle leads. The HV interval was measured from the His bundle to the earliest ventricular activity in any intracardiac or surface lead. A paper speed of 100 mm . s \(^{-1}\) was used.

All intracardiac ECG recordings were analysed by two cardiologists and the level of block was determined without any knowledge of the outcome of the RR index test. Atrioventricular nodal and His-Purkinje atrioventricular block were defined as an atrioventricular block located above or below the bundle of His, respectively.

RR-index

The RR index was constructed by calculating the following fraction (Fig. 1):

$$\frac{\text{RR interval after the atrioventricular block} - \text{RR interval before the atrioventricular block}}{\text{RR interval before the atrioventricular block}}$$

The RR interval was measured in lead V\(_1\) from the onset of the QRS complex to the onset of the next consecutive complex.

Statistical methods

Descriptive statistics and graphic methods were used to characterize data. Fisher’s exact test was used for comparisons of proportions. Comparisons of continuous, normally distributed variables were made using Students’ t-test. The Mann–Whitney test was used for data which did not have normal distribution. All analyses were performed using the statistical package of JMP\(^\text{®}\) version 3.0 (SAS Institute). Normally distributed data are expressed as mean value ± standard deviation (SD) and not normally distributed data as the median value. A P value <0.05 was considered statistically significant.

The study was approved by the Ethics Committee of the Karolinska Hospital.

Results

RR index

Incremental atrial pacing was performed twice, in the basal state, in the 98 patients, with exception of those who developed atrial fibrillation or who experienced discomfort. Thus, in all, 348 sequences of incremental atrial pacing were studied; 189 in the basal state, 23 after atropine and 136 after disopyramide infusion (Table 1). In 25 (7%) of the recordings the block was located in the His–Purkinje system, in 269 (77%) in the atrioventricular node and in 54 (16%) the localization was not possible to
**Figure 1** Examples of incremental atrial pacing in two patients with left bundle branch block. In the upper panel (a) the intra-cardiac registration shows an atrioventricular nodal block, i.e. a block above the bundle of His. In the lower panel (b) the atrial pacing results in a His-Purkinje block, here situated below the bundle of His. Below the intra-cardiac recordings the corresponding ladder diagrams show the PP, AH and RR intervals. The RR index is calculated as the difference in RR intervals immediately before (A) and after (B) the block divided by the RR interval before the block (A). The RR index is thus calculated as (494-380)/380=0.30 in (a) (atrioventricular nodal block) and as (770-398)/398=0.93 in (b) (His-Purkinje block). VA=Chest-lead V; HRA=high right atrium registration; HBE=proximal His potential registration; RV=right ventricular registration; S=stimuli; A=atrial potential; H=His potential; V=ventricular potential.

determine. All His–Purkinje blocks were located below the bundle of His and there were no intra-Hisian blocks. The median RR index was 0.98 (range, 0.88–1.02) in recordings with a His–Purkinje block and 0.49 (range, 0.11–0.89) in recordings with atrioventricular nodal block (P<0.001) (Fig. 2). The corresponding value was 0.38 (range, 0.05–0.92) in recordings without an identifiable His potential during atrial pacing, 0.42 (range, 0.11–0.81) in the basal state and 0.45 (range, 0.04–0.92) in patients challenged with disopyramide (ns). An RR index of ≥0.85 had a sensitivity of 100% and a specificity of 99% for the identification of a His–Purkinje block. Both the sensitivity and specificity of the test was 100% in the basal state. The two false-positive tests appeared after disopyramide infusion, i.e. showing a specificity of 98%.

The 25 recordings showing a His–Purkinje block appeared in 12 patients. All these recordings had an RR index ≥0.85. Two additional patients, one with an atrioventricular nodal block and the other with an uncertain localization of the block, had an RR index ≥0.85 (Fig 2). In neither of these two patients was there evidence of dual atrioventricular nodal physiology, defined as a jump in atrioventricular node conduction of ≥50 ms for a 10 ms decrement in the coupling interval (S1S2), atrioventricular nodal echo beat(s) or the induction of atrioventricular node reentrant tachycardia.

The reproducibility of the RR index was high in patients with His–Purkinje block (Fig. 3). In patients with atrioventricular nodal block however, there was a substantial variation in the RR index between the first and second pacing session.
Table 1 Result of the electrophysiological study in the total study population (n=98). In 84 patients the study was repeated after a pharmacological provocation with atropine (n=12) or disopyramide (n=72)

<table>
<thead>
<tr>
<th></th>
<th>Basal state</th>
<th>Atropine</th>
<th>Disopyramide</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>98</td>
<td>12</td>
<td>72</td>
</tr>
<tr>
<td>Dose; mean mg (range)</td>
<td></td>
<td>1.5 (1-2)</td>
<td>141 (100-150)</td>
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<tr>
<td>AH interval; mean ms (range)</td>
<td>90 (37-168)</td>
<td>87 (68-112)</td>
<td>91 (54-188)</td>
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<tr>
<td>AH diff vs baseline; ms</td>
<td></td>
<td>- 17</td>
<td>3</td>
</tr>
<tr>
<td>HV; median ms (range)</td>
<td>54 (32-155)</td>
<td>59 (41-103)</td>
<td>66 (35-150)</td>
</tr>
<tr>
<td>CL at AV block; median ms (range)</td>
<td>365 (257-630)</td>
<td>343 (266-427)</td>
<td>385 (269-715)</td>
</tr>
<tr>
<td>AVN-ERP; mean (range)</td>
<td>328 (200-580)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of AP sequences</td>
<td>189</td>
<td>23</td>
<td>136</td>
</tr>
<tr>
<td>AV nodal block n (%)</td>
<td>155 (82)</td>
<td>21 (88)</td>
<td>93 (68)</td>
</tr>
<tr>
<td>His-Purkinje block n (%)</td>
<td>5 (3)</td>
<td>0</td>
<td>20 (15)</td>
</tr>
<tr>
<td>Not possible to locate n (%)</td>
<td>29 (15)</td>
<td>2 (12)</td>
<td>23 (17)</td>
</tr>
</tbody>
</table>

AP = atrial pacing; AV = atrioventricular; AVN-ERP = effective refractory period of the atrioventricular node at a basic drive of 100 beats min⁻¹; CL = cycle length; diff = difference; — = not applicable or not done. Reference limits: AVN-ERP: 230 ± 30 ms, AH: 60-120 ms, HV: 35-55 ms.

Figure 2 Quantile box plots showing the individual values of the RR index for atrioventricular block induced by incremental atrial pacing resulting in His–Purkinje block (n=25), atrioventricular nodal block (n=269) and in a non-localizable block (n=54). The quantile boxes show the group medians as a line across the middle and the quartiles (25th and 75th percentiles) as their ends. The 10th and 90th percentiles are shown as lines above and below the boxes.

Atrioventricular nodal function

The mean ± SD atrioventricular node–effective refractory period was 346 ± 120 ms in patients with a His–Purkinje block, 327 ± 79 ms in patients with atrioventricular nodal block and 308 ± 77 ms in patients with uncertain level of block (P=ns). The corresponding values of the mean AH interval at baseline was 83 ± 22 ms, 91 ± 28 ms and 102 ± 20 ms (P=ns). Atrioventricular node dysfunction, defined as atrioventricular node–effective refractory period ≥430 ms or AH > 120 ms [11], was found in three (25%), 15 (19%) and one (17%), respectively (P=ns). Three (21%) and 16 (19%) of the patients with an RR index above or below 0.85, respectively, had atrioventricular node dysfunction (P=ns). The median cycle length at which atrioventricular block was induced was longer in patients with the His–Purkinje block (440 ms, range, 356–850 ms) than in patients with atrioventricular nodal block or not localizable block (374 ms, range, 257–631 ms and 341 ms, respectively).
RR index test for differentiating atrioventricular nodal block from His-Purkinje block

Figure 4 A Rosenblueth ladder diagram illustrating a possible explanation of the RR index at incremental atrial pacing. Panel A shows an example of atrioventricular nodal block whereas panel B shows His-Purkinje block. In panel A a delay is shown when the first to third stimuli reach the relative refractory period of the atrioventricular node (in line shadow). The fourth stimulus falls within the effective refractory period (in cross hatch shadow) and is blocked in the atrioventricular node. The next stimulus falls outside both the relative and effective refractory period, resulting in a short AH interval and hence, a short RR interval. Since the stimulus preceding the block has a long AH interval the resulting RR index is low (0-19). In panel B a His-Purkinje block is induced by incremental atrial pacing. All stimuli fall outside both the effective and relative atrioventricular nodal refractory period, but the third stimulus is blocked within the His-Purkinje system. Since the AH interval is the same in the beat before and after the block, the RR index is high (0-90).

range, 263–643 ms, respectively) (P<0.01). There was, however, considerable overlap between the groups and this parameter had a low predictive value for the differentiation of atrioventricular nodal block from His-Purkinje atrioventricular block.

Complications
Six patients had pacing-induced atrial fibrillation which resolved spontaneously within 30 min in five and after intravenous disopyramide in one. One patient had a symptomatic fall in systolic blood pressure from 120 to 85 mmHg. This appeared after disopyramide infusion and was unsuccessfully treated with saline.

Discussion
This study shows that a simple test (RR index) based on RR interval measurements of atrioventricular block induced by incremental atrial pacing, can be helpful in differentiating between block in the atrioventricular node and block in the His-Purkinje system in patients with bifascicular block.

Hypothesis behind the RR index
The normal response to incremental atrial pacing is a smooth increase in the atrioventricular conduction time which is mainly due to decremental properties of the antegrade atrioventricular nodal conduction. In consequence, the AH interval will represent an increasingly larger proportion of the total conduction time from the atrial stimulus to the ventricle (Figs 1 and 4). Intra-atrial and His-Purkinje conduction intervals will, however, remain relatively constant, since they are affected considerably less, if at all, by changes in heart rate. Experimental data suggest that atrioventricular node conduction block usually occurs in the N cell zone. In general, these cells, as well as cells in the more proximal AN zone, have shorter refractory periods than cells in the NH zone, which is located closer to the His bundle. A block in the N zone would therefore allow the next stimulus a relatively rapid atrioventricular node conduction, resulting in a short AH interval, a short RR interval and, as a consequence, a low RR index. Atrioventricular nodal block showed a wide range of RR index values and great variation in the RR index between two consecutive pacing sessions (Fig. 3). This might be due to inter- and intra-individual fluctuations.
in the autonomic nervous system. It is also possible that stimuli resulting in an RR index in the upper range reflect penetration of the deeper zones of the atrioventricular node, whereas a low value may reflect penetration of the AN zone only. Since a block in the His–Purkinje system would follow full depolarization of the atrioventricular node, full recovery would be shortened only by the His–Purkinje conduction time (HV interval) (Fig. 4). This is also reflected by the high reproducibility of the RR index in patients with His–Purkinje block (Fig. 3).

Sensitivity and specificity of the RR index

This study suggests that an RR index \( \geq 0.85 \) has 100% sensitivity and 99% specificity for the identification of a His–Purkinje block. However, several mechanisms that can cause both false-negative and false-positive findings have to be considered.

Dhingra et al. showed that a pacing-induced block distal to the His bundle during intact atrioventricular nodal conduction can show two patterns\(^{16,13} \). In the vast majority, the block showed a similar pattern to the recording shown in Fig. 1(b) i.e. a constant HV interval in the beats preceding the His–Purkinje block. In a few cases, progressive prolongation of the HV interval was documented. If significant variations in the HV interval should occur, resulting in a larger proportion of the RR interval, the RR index would be lower than expected. Only minor changes in the HV interval, reflected as an RR index between 0.85 and 1.00, were, however, found in this study.

A prerequisite for His–Purkinje block during atrial pacing is the exposure of the distal conduction system to impulses penetrating the atrioventricular node. Atrioventricular node dysfunction could therefore mask a defective third fascicle in patients with bifascicular block by limiting the rate to which the His–Purkinje system is exposed, thereby resulting in a falsely low RR index. This possibility must be considered but did not seem to be a significant problem in the present study. Firstly, a significantly lower stimulation rate was usually required for the induction of His–Purkinje block and secondly there were no differences in the mean effective refractory period of the atrioventricular node or mean AH interval, between patients showing atrioventricular nodal and His–Purkinje block, respectively.

Previous studies have shown that up to 70% of both spontaneous and pacing-induced atrioventricular nodal block show an atypical Wenckebach periodicity\(^{14,15} \). However, the vast majority of these will not cause a marked prolongation of the RR interval after the block and will therefore not result in an RR index \( \geq 0.85 \). El-Sherif et al. have, however, reported the occurrence of atypical Wenckebach periodicity, simulating Mobitz II atrioventricular block\(^{16,17} \). This would probably result in a false-positive RR index test. The majority of the pseudo-Mobitz II blocks reported in their study did, however, occur in patients with acute myocardial infarction and in patients without intraventricular conduction defects and furthermore all occurred spontaneously.

The existence of dual atrioventricular nodal physiology\(^{18,19} \) with a sudden change in atrioventricular node conduction (creating a discontinuous curve) may cause both false-positive and negative findings depending upon the refractoriness of the fast and slow pathways in relation to the refractoriness of the His–Purkinje system. This possibly confounding factor did not seem to influence the results of the present study.

It is of critical importance to ensure that stable capture is achieved during atrial pacing. A non-captured beat might simulate an atrioventricular block and can result in both a falsely low and a falsely high RR index. Moreover, a false-positive finding can also be caused by two consecutive atrial beats which are blocked in the atrioventricular node. This did not occur in this study but to avoid this risk an upper cut off value of the RR index may be necessary. The present data suggest that an RR index above 1.1 does not occur in patients with His–Purkinje block and may be used without the risk of obtaining false negative tests.

Possible applications

His–Purkinje block, induced by incremental atrial pacing, is a rare but specific finding for the prediction of impending high-degree atrioventricular block in patients with bifascicular block, both in the basal state\(^{2,5,9} \) and after pharmacological provocation with disopyramide\(^{21} \). In order to localize the level of atrioventricular block, an invasive electrophysiological study during which, His bundle potential is recorded, is required. In some patients, however, localization of His bundle potential is difficult, especially during atrial pacing at high rates during which His potential can be hidden within the atrial or ventricular deflection. Our results suggest that this is not uncommon (16% of our recordings). Some of these problems may be overcome by the use of the RR index, and the test makes it possible to perform incremental atrial pacing, with or without pharmacological provocation, without intracardiac recording facilities.

Another possible target group for the RR index test is patients with an implanted AAI-pacemaker who have a newly developed bundle branch block\(^{29} \). By performing rapid atrial pacing through the pacemaker programmer, a risk evaluation can be performed.

Risk analysis might also be performed by incremental atrial pacing through an oesophageal lead\(^{11} \). This technique allows the atrium to be stimulated non-invasively. According to the literature, oesophageal pacing has not been used for this purpose and has to be evaluated in future studies before any conclusions can be made regarding the feasibility of the RR index being used in this application.

Limitations

Although this study presents data from a relatively large number of pacing-induced atrioventricular blocks, only a limited number of these were localized to the His-Purkinje system. Further studies, involving a larger number of patients are therefore needed and the proposed criteria of the RR index have to be prospectively studied.

References