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Syncope Due to Idiopathic Paroxysmal Atrioventricular Block

Long-Term Follow-Up of a Distinct Form of Atrioventricular Block

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Objectives
We present data on patients with syncope due to paroxysmal atrioventricular (AV) block unexplainable in terms of currently known mechanisms.

Background
Paroxysmal AV block is known to be due to intrinsic AV conduction disease or to heightened vagal tone.

Methods
We evaluated 18 patients presenting with unexplained syncope who had: 1) normal baseline standard electrocardiogram (ECG); 2) absence of structural heart disease; and 3) documentation, by means of prolonged ECG monitoring at the time of syncopal relapse, of paroxysmal third-degree AV block with abrupt onset and absence of other rhythm disturbances before or during the block.

Results
The study group consisted of 9 men and 9 women, mean age 55 ± 19 years, who had recurrent unexplained syncope for 8 ± 7 years and were subsequently followed up for as long as 14 years (4 ± 4 years on average). The patients had no structural heart disease, standard ECG was normal, and electrophysiological study was negative. In all patients, prolonged ECG monitoring documented paroxysmal complete AV block with 1 or multiple consecutive pauses (mean longest pause: 9 ± 7 s at the time of syncope; AV block occurred without P-P cycle lengthening or PR interval prolongation. During the observation time, no patient had permanent AV block; on permanent cardiac pacing, no patient had further syncopal recurrences.

Conclusions
Common clinical and electrophysiological features define a distinct form of syncope due to idiopathic paroxysmal AV block characterized by a long history of recurrent syncope, absence of progression to persistent forms of AV block, and efficacy of cardiac pacing therapy. (J Am Coll Cardiol 2011;58:000–0)

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Paroxysmal third-degree atrioventricular (AV) block is a known cause of syncope. Paroxysmal AV block that occurs in patients with underlying heart disease and/or abnormal standard electrocardiogram (ECG) is usually regarded as a manifestation of an intrinsic disease of the AV conduction system (Stokes-Adams attack). This is usually confirmed by abnormal electrophysiological findings (1,2). Well-defined clinical and electrophysiological features allow differentiating intrinsic AV block from the other known form of block, namely, vagal (extrinsic) paroxysmal AV block. Differentiation between the often benign and reversible causes of vagal AV block from intrinsic AV block is of practical importance because the benefit of permanent cardiac pacing for vagal AV block is controversial (3,4).

In this study, we present data on patients with syncope due to paroxysmal AV block unexplainable in terms of currently known mechanisms.

Methods
In this 4-center study, we evaluated 18 patients presenting with unexplained syncope who had: 1) normal baseline standard ECG; 2) absence of structural heart disease; and 3) documentation, by means of prolonged ECG monitoring at the time of syncopal relapse, of paroxysmal third-degree AV block with abrupt onset (and delayed emergence of an adequate escape rhythm) and absence of other rhythm disturbances before or during the block (type 1C according to the ISSUE [International Study of Syncope of Uncertain Etiology] study classification [5]).
These patients underwent a full cardiological work-up that excluded structural heart disease. In particular, a conventional invasive electrophysiological evaluation, which included rapid atrial pacing and ajmaline drug challenge, was performed in 15 patients; 3 patients denied their consent for the examination. Further additional nonconventional electrophysiological tests included measurement of baseline adenosine plasma level (APL) as described previously (J.C. Deharo et al., personal communication, 2011) (6–8) and adenosine or adenosine triphosphate (ATP) test (9–11). An increased susceptibility to the ATP test has been suspected in patients with syncope due to paroxysmal AV block (9). Syncope work-up was completed by means of tilt-table testing and carotid sinus massage.

The APL was also determined in 9 control patients (6 men and 3 women, mean age 58 ± 17 years) with syncope due to reflex long pauses (mean 20 ± 16 s) due to sinus arrest documented by implantable loop recorder, and in 81 healthy subjects matched for age and sex.

Data are reported as mean ± SD or as median (interquartile range [IQR]), as appropriate. Comparison between 2 continuous variables with a non-Gaussian distribution was performed by applying the Mann-Whitney nonparametric test.

### Results

The study group consisted of 9 men and 9 women (mean age 55 ± 19 years) who had had recurrent unexplained syncope and pre-syncpe for 8 ± 7 years (median 6 years, IQR: 3 to 12 years, range 0 to 20 years) (Table 1). Most syncopal episodes were unpredictable, in that prodromes were absent or very short (a few seconds of dizziness or blurred vision). Only 3 patients had some episodes with features that suggested autonomic activation: during a meal preceded by prodromes (Patient #4), triggered by unexplained cough or by emotion (Patient #11), and preceded by nausea and prodromes (Patient #16). The patients did not have structural heart disease, and standard ECG was normal. Prolonged ECG monitoring (implantable loop recorder in 10 patients, Holter in 5 patients, and in-hospital telemetry in 3 patients) at the time of syncope or pre-syncpe documented paroxysmal complete AV block with 1 or multiple consecutive pauses (longest pause 9 ± 7 s) due to absence or depression of escape rhythm in all patients; AV block occurred without P-P cycle lengthening (n = 12) or with minimal P-P cycle lengthening (n = 6); PR interval remained stable before and at the end of the pause (Figs. 1, 2, and 3).

One patient had advanced AV block, which persisted for 2 days, followed by first-degree AV block for a few days and then normal conduction. An electrophysiological study performed at the time of first-degree AV block showed impaired AV nodal conduction. Multiple episodes of AV block (2 to 20) were also documented in 11 patients.

### Table 1

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Age (yrs), Sex</th>
<th>Total No.</th>
<th>Duration (yrs)</th>
<th>Prodromes, Autonomic Activation, Triggers</th>
<th>Diagnostic Tool</th>
<th>Max Pause, s</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>73, M</td>
<td>20</td>
<td>8.0</td>
<td>No</td>
<td>ILR</td>
<td>5.0</td>
</tr>
<tr>
<td>2</td>
<td>85, F</td>
<td>4</td>
<td>1.0</td>
<td>No (all while sitting)</td>
<td>ILR</td>
<td>13.0</td>
</tr>
<tr>
<td>3</td>
<td>69, M</td>
<td>2</td>
<td>0.5</td>
<td>No</td>
<td>ILR</td>
<td>3.5</td>
</tr>
<tr>
<td>4</td>
<td>63, F</td>
<td>3</td>
<td>7.0</td>
<td>Yes (meal, prodromes)</td>
<td>ILR</td>
<td>5.0</td>
</tr>
<tr>
<td>5</td>
<td>50, F</td>
<td>20</td>
<td>20.0</td>
<td>No</td>
<td>ILR</td>
<td>22.0</td>
</tr>
<tr>
<td>6</td>
<td>63, F</td>
<td>6</td>
<td>13.0</td>
<td>No</td>
<td>ILR</td>
<td>10.0</td>
</tr>
<tr>
<td>7</td>
<td>66, F</td>
<td>25</td>
<td>8.0</td>
<td>No</td>
<td>ILR</td>
<td>28.0</td>
</tr>
<tr>
<td>8</td>
<td>57, F</td>
<td>Very frequent</td>
<td>5.0</td>
<td>No</td>
<td>In-hospital telemetry</td>
<td>4.5</td>
</tr>
<tr>
<td>9</td>
<td>68, M</td>
<td>6</td>
<td>18.0</td>
<td>No</td>
<td>ILR</td>
<td>17.0</td>
</tr>
<tr>
<td>10</td>
<td>62, M</td>
<td>4</td>
<td>2.0</td>
<td>No (1 while driving)</td>
<td>ILR</td>
<td>8.0</td>
</tr>
<tr>
<td>11</td>
<td>70, F</td>
<td>100</td>
<td>20.0</td>
<td>Yes (tussive, emotional)</td>
<td>7-day Holter</td>
<td>8.0</td>
</tr>
<tr>
<td>12</td>
<td>20, M</td>
<td>4</td>
<td>4.0</td>
<td>No</td>
<td>In-hospital telemetry</td>
<td>3.6</td>
</tr>
<tr>
<td>13</td>
<td>41, M</td>
<td>10</td>
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<td>No</td>
<td>Holter</td>
<td>3.4</td>
</tr>
<tr>
<td>14</td>
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<td>21</td>
<td>4.0</td>
<td>No</td>
<td>Holter</td>
<td>11.0</td>
</tr>
<tr>
<td>15</td>
<td>13, M</td>
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<tr>
<td>16</td>
<td>49, F</td>
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<tr>
<td>17</td>
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<td>4.5</td>
</tr>
<tr>
<td>18</td>
<td>26, F</td>
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<td>16.0</td>
<td>No</td>
<td>In-hospital telemetry</td>
<td>5.0</td>
</tr>
</tbody>
</table>
in whom monitoring was continued after the first documented syncope; these were always similar to the first documented episode.

After the diagnosis, the patients were followed up for a total of 4 ± 4 years (range 0.6 to 14 years). Seventeen patients underwent permanent dual-chamber cardiac pacing, and no patient had recurrence of syncope. The total time from the first syncopal symptom to the end of follow-up was 12 ± 8 years (range 1.6 to 34 years). During this period, no patient had permanent AV block.

**Laboratory findings.** Electrophysiological study did not show any impairment of AV conduction in 14 patients; in 1 of these, mild sinus dysfunction was detected. The median baseline APL of these patients was significantly lower than that found in the age- and sex-matched population of 81 healthy subjects: 0.33 μM (IQR: 0.20 to 0.56 μM) versus 0.49 μM (IQR: 0.38 to 0.68 μM, p = 0.017). The median APL value of the patients was also 4-fold lower than that found in 9 control patients with syncope due to reflex sinus arrest (1.2 μM [IQR: 1.0 to 1.7 μM]; p = 0.001) (Fig. 4). In 15 (83%) patients with paroxysmal AV block, the rapid intravenous injection of 18 mg adenosine or 20 mg ATP caused complete AV block similar to the spontaneous AV block and a mean maximum pause of 10 ± 6 s (Table 1, Fig. 3B). Finally, tilt-table testing induced a vasovagal syncope in 7 (41%) of cases, but never reproduced AV block, and carotid sinus massage was negative in all patients in whom it was performed.

**Discussion**

The common clinical and electrophysiological features of these patients define a distinct form of syncope characterized by a long history of recurrent syncope due to idiopathic paroxysmal AV block with long pauses, absence of cardiac and ECG abnormalities, absence of progression to persistent forms of AV block, and efficacy of cardiac pacing therapy. These patients have low baseline APL values and show an increased susceptibility to exogenous adenosine.

Similar ECG features have been occasionally described in individual patients in clinical studies (9,11,12) and in a few case reports (13–16); no follow-up is reported.

In our patients, the paroxysmal AV block had different clinical and electrophysiological features from those of the 2 other known types of paroxysmal AV block: intrinsic AV block due to AV conduction disease and extrinsic vagal AV block.

Intrinsic AV block due to AV conduction disease was unlikely in our population. The absence of any evidence of cardiac abnormalities, the young age of several of these patients, and the outcome showing no progression of the block toward permanent forms for several years argue against an intrinsic cardiac etiology. Furthermore, the AV block was never initiated by atrial, His, or ventricular premature extrasystole, increased heart rate (tachydependent AV block), or decreased heart rate (brady-dependent AV block), all features that support a diagnosis of intrinsic AV block (1,2).

The clinical features of our patients were also different from those of a typical population of patients affected by vasovagal syncope. Specifically, historical findings of autonomic activation, triggering, and predisposing factors that could suggest a diagnosis of reflex syncope were encountered only in 3 of our patients, whereas the etiology remained

**Table 1 Continued**

<table>
<thead>
<tr>
<th>APL (μM)</th>
<th>ATP Test: AVB (Max Pause, s)</th>
<th>EPS</th>
<th>Tilt Table Testing</th>
<th>Carotid Sinus Massage</th>
<th>PM Therapy</th>
<th>Follow-Up</th>
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<td>0.91</td>
<td>Yes (7.5)</td>
<td>Normal</td>
<td>DOH</td>
<td>Not done</td>
<td>Yes</td>
<td>4.4</td>
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<td>0.45</td>
<td>Sinus arrest</td>
<td>Mild SND</td>
<td>Mixed</td>
<td>Negative</td>
<td>Yes</td>
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<tr>
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<td>Yes (8.0)</td>
<td>Normal</td>
<td>Mixed</td>
<td>Negative</td>
<td>Yes</td>
<td>8.0</td>
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<td>Yes (3.3)</td>
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<td>Mixed</td>
<td>Negative</td>
<td>Yes</td>
<td>1.7</td>
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<td>0.89</td>
<td>Yes (11.0)</td>
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<td>Negative</td>
<td>Negative</td>
<td>Yes</td>
<td>14.0</td>
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<tr>
<td>0.40</td>
<td>Yes (8.6)</td>
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<td>Negative</td>
<td>Negative</td>
<td>Yes</td>
<td>10.0</td>
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<tr>
<td>0.20</td>
<td>Yes (7.6)</td>
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<td>Negative</td>
<td>Negative</td>
<td>Yes</td>
<td>2.0</td>
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<td>0.29</td>
<td>Yes (8.0)</td>
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<td>Not done</td>
<td>Not done</td>
<td>No</td>
<td>1.7</td>
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<tr>
<td>0.36</td>
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<tr>
<td>0.70</td>
<td>Yes (5.0)</td>
<td>Not done</td>
<td>Negative</td>
<td>Negative</td>
<td>Yes</td>
<td>5.0</td>
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<tr>
<td>0.38</td>
<td>Yes (10.0)</td>
<td>Normal</td>
<td>Negative</td>
<td>Negative</td>
<td>Yes</td>
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<tr>
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<td>Yes</td>
<td>5.6</td>
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<tr>
<td>0.11</td>
<td>Yes (13.7)</td>
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<td>Negative</td>
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<td>2.3</td>
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<tr>
<td>0.89</td>
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<td>Negative</td>
<td>Yes</td>
<td>10.7</td>
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<tr>
<td>0.74</td>
<td>Yes (18.0)</td>
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<td>1.1</td>
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<tr>
<td>0.34</td>
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<td>Yes</td>
<td>1.3</td>
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<tr>
<td>0.12</td>
<td>Yes (25.0)</td>
<td>Normal</td>
<td>Sinus arrest</td>
<td>Negative</td>
<td>Yes</td>
<td>0.6</td>
</tr>
</tbody>
</table>

*Patient #8 had advanced-degree atrioventricular block (AVB) that persisted for 2 days, then first-degree AVB for few days, then normal conduction. An electrophysiological study (EPS) performed at the time of the block showed impaired AV nodal conduction.

APL = adenosine plasma level; ATP = adenosine triphosphate; DOH = delayed orthostatic hypotension; ILR = implantable loop recorder; Max = maximum; PM = pacemaker; SND = sinus node disease.
Figure 1 Case #14

(A, B) Holter recording of 2 episodes of spontaneous syncope that occurred a few minutes apart. The 2 episodes were very similar and were characterized by sudden-onset complete atrioventricular (AV) block without changes in P-P cycle length, which constantly remained 720 ms and long ventricular asystole of 7 s and 11 s (top and bottom, compressed traces, respectively). Figure illustration by Craig Skaggs.

Figure 2 Case #10

The 4 strips are continuous and show a spontaneous syncope recorded by implantable loop recorder. Initial minimal sinus slowing (P-P cycle increased by 80 ms) was followed by 2:1 atrioventricular (AV) block and finally complete AV block with a very long asystolic pause. During AV block, the P-P cycle progressively shortened, indicating a compensatory reflex sympathetic activation. Figure illustration by Craig Skaggs.
unexplained in the others. Also, the electrophysiological features of our patients were against a vagally mediated AV block. Indeed, a classic vagal effect on the conduction system includes gradual slowing of the sinus rate (P-P interval) and AV conduction (prolonging PR), which are occasionally followed by sinus arrest or complete AV block. The 2 conditions frequently coexist, indicating a simultaneous vagal action on sinus node and AV node. Even when a more prominent AV response occurs, vagally mediated AV block is usually preceded by significant PR prolongation or Wenckebach; the P-P interval is prolonged markedly also during asystole, and there is significant PR prolongation on resumption of AV conduction (1,4,5,17). These features were absent in our patients, who were affected by abrupt-onset AV block without significant rhythm disturbances before or during the attack (type 1C block).

Paroxysmal type 1C AV block is very rare during tilt-induced vasovagal syncope. Apart from 2 case reports (14,18), AV block with a constant P-P cycle has never been observed in large series of tilt-table tests (17,19). In the present study, tilt-table testing, which induced a vasovagal syncope in 7 cases, never reproduced AV block. Carotid sinus massage was invariably negative. In addition, low APL values clearly differentiated our patients from patients with documented spontaneous reflex sinus arrest, who had a median APL value 4 times higher than patients with AV block (Fig. 4). High APL values seem to characterize vasovagal syncope as they were also found in 3 studies.
involving patients with a diagnosis of vasovagal syncope confirmed by positive tilt-table testing (J.C. Deharo et al., personal communication, 2011) (6,7). Thus, a different plasmatic adenosine background seem to be present in patients with idiopathic AV block and in patients with vasovagal syncope. Finally, permanent cardiac pacing was completely successful in preventing syncopal recurrences during long-term follow-up. This suggests that paroxysmal AV block was the main determinant of syncope in our patients. Conversely, cardiac pacing has been reported to be less efficacious in patients affected by reflex cardioinhibitory syncope, even if a spontaneous asystolic reflex has been documented, with syncope recurring in 9% to 45% of patients (3,4). The cause of persistence of syncopal recurrence in reflex syncope is attributed to the coexistence of a vasodepressor reflex, which, to some degree, is present in virtually all patients.

**Pathophysiological observations.** We found that our patients had a low baseline APL value (compared with control subjects and with patients with reflex asystolic syncope) and a rate of positive ATP test much higher than that found in the literature in normal control subjects (9) and in patients with unexplained syncope (9–12,20), indicating an increased susceptibility of the AV node to adenosine. These observations may lead to hypothesize some relationship between the adenosine pathway and the genesis of the AV block.

The effect of adenosine on the AV node is mainly due to the stimulation of high-affinity A1 receptors, which are much more numerous in the AV node than in the sinoatrial node (21–23). Like many other cell surface receptors, the number of cardiac adenosine A1 receptors undergoes up-regulation and down-regulation when cardiac tissues are chronically exposed to low or elevated concentrations of adenosine receptor agonist (i.e., adenosine), respectively. A transient release of endogenous adenosine could be sufficient to block conduction in the AV node when a high number of free high-affinity A1 receptors in the AV node are available (low-APL patients). The cause of the transient release of endogenous adenosine responsible for paroxysmal AV block in our patients is unknown. Adenosine is a ubiquitous substance, which is released under several physiological and pathological conditions (e.g., in the case of myocardial hypoxia or during reflex beta-adrenergic stimulation) (24,25). Even if a role of the adenosine pathway in the genesis of the AV block may be possible, these data are insufficient to prove a causal relationship. Therefore, the mechanism of the block in our patients remains largely unexplained (idiopathic AV block). The above observations might be of interest for the planning of future studies.

**Study limitations.** Three patients had historical features that suggest the activation of vasovagal or situational reflexes. Seven patients had a vasovagal response during tilt-table testing. Apart these features, these patients were indistinguishable from the others. The absence of sinus slowing along with AV block does not definitely rule out some role of exogenous hypervagotonia in causing the block in these patients. Probably are the very different APL values that differentiate better the patients with idiopathic AV block from patients with typical vasovagal syncope. In some patients, the follow-up period after pacemaker implantation was too short to allow evaluating the efficacy of pacing therapy in preventing symptomatic recurrences.

**Conclusions**

In clinical practice, paroxysmal AV block without or with minimal changes in the P-P cycle, as was observed in our study patients, is usually regarded as a manifestation of an intrinsic disease of the AV conduction system, and in accordance with current guidelines (26), a diagnosis of cardiac syncope (primary arrhythmia) is made. Conversely, on the basis of their clinical features and the absence of any detectable cardiac abnormality, our patients would probably have been categorized as possibly affected by an atypical form of neurally mediated syncope if they had not had the rather fortuitous documentation of paroxysmal AV block at the time of syncope (26). Therefore, 2 opposite diagnoses could be made in the same patients, depending on whether paroxysmal AV block during a spontaneous attack is documented on ECG. We were able to give an alternative explanation.

How frequent is syncope due to idiopathic AV block? Type 1C block was found to be present in 8% of syncope patients with normal ECG and absence of structural heart disease (corresponding to 15% of those who had ECG documentation of syncope) (11). We can only speculate that these figures may represent the prevalence of this new syndrome among patients without structural heart disease who are affected by unexplained syncope. However, a prospective study is needed to confirm this hypothesis.

Given that ECG documentation of idiopathic AV block is the gold standard for diagnosis, is there some other test that could anticipate diagnosis? The adenosine test appeared to be sensitive enough to identify the patients with idiopathic AV block in this study, but it showed a very low specificity in other studies in which there was a lack of correlation between the responses to the test and the mechanism of spontaneous syncope documented by implantable loop recorder (11,12). There is not a clear-cut cutoff of APL value between idiopathic AV block patients and normal control subjects. In patients with unexplained syncope, normal ECG, and absence of structural heart disease, low-to-normal APL values suggest an idiopathic AV block whereas high APL values suggest a typical reflex syncope. That is probably likely for patients (30% of our population) who have an APL value <0.24 μM, which is the fifth lower percentile in normal healthy subjects. However, the specificity of APL value in identifying idiopathic AV block is unknown and a matter of future studies.
REFERENCES


Key Words: adenosine • AV block • syncope • ECG monitoring • electrophardiography.
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