

Syncope and Idiopathic (Paroxysmal) AV Block

Michele Brignole, MD, FESC^{a,*},
Jean-Claude Deharo, MD, FESC^b, Regis Guieu, MD^c

KEYWORDS

• Atrioventricular block • Implantable loop recorder • ECG • Syncope

KEY POINTS

- Syncope due to idiopathic AV block is characterized by: 1) ECG documentation (usually by means of prolonged ECG monitoring) of paroxysmal complete AV block with one or multiple consecutive pauses, without P-P cycle lengthening or PR interval prolongation, not triggered by atrial or ventricular premature beats nor by rate variations; 2) long history of recurrent syncope without prodromes; 3) absence of cardiac and ECG abnormalities; 4) absence of progression to persistent forms of AV block; 5) efficacy of cardiac pacing therapy.
- The patients affected by idiopathic AV block have low baseline adenosine plasma level values and show an increased susceptibility to exogenous adenosine. The APL value of the patients with idiopathic AV block is much lower than patients affected by vasovagal syncope who have high adenosine values.

DIAGNOSIS OF IDIOPATHIC AV BLOCK

Syncope due to idiopathic atrioventricular (AV) block (**Box 1**) is a distinct clinical form of syncope characterized by common clinical and electrophysiologic features¹:

- Electrocardiographic (ECG) documentation (usually by means of prolonged ECG monitoring) of idiopathic paroxysmal complete AV block with one or multiple consecutive pauses; AV block occurs without P-P cycle lengthening or PR interval prolongation and is not triggered by atrial or ventricular premature beats nor by rate variations (**Fig. 1**)
- Long history of recurrent syncope without prodromes

- Absence of cardiac and ECG abnormalities
- Absence of progression to persistent forms of AV block
- Efficacy of cardiac pacing therapy

Patients affected by idiopathic AV block have low baseline adenosine plasma level (APL) values and show an increased susceptibility to exogenous adenosine. In one study,¹ the median baseline APL of these patients was significantly lower than that found in the age-matched and sex-matched population of 81 healthy subjects: 0.33 μ M (interquartile range 0.20–0.56) versus 0.49 μ M (0.38–0.68) ($P = .017$). APL values of patients with idiopathic AV block are much lower than those of patients affected by typical vasovagal syncope and patients with positive tilt table

The authors have nothing to disclose.

^a Department of Cardiology, Arrhythmologic Center, Ospedali del Tigullio, Via Don Bobbio 25, Lavagna 16033, Italy; ^b Department of Cardiology, Timone University Hospital, 264, rue Saint Pierre 13385, Marseille, France;

^c Laboratory of Biochemistry and Molecular Biology, Timone University Hospital, Unité Mixte de Recherche Ministère de la Défense, Aix Marseille Université, Boulevard P Dramard, Marseille 13015, France

* Corresponding author.

E-mail address: mbrignole@ASL4.liguria.it

Card Electrophysiol Clin 5 (2013) 487–493

<http://dx.doi.org/10.1016/j.ccep.2013.08.008>

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Box 1**Definitions**

Idiopathic (paroxysmal) AV block is defined as a paroxysmal third-degree AV block that displays an abrupt onset and no other rhythm disturbances before or during the block and that occurs in patients with a normal heart and normal ECG

Syncope due to idiopathic paroxysmal AV block is defined as syncope caused by long asystolic pauses due to complete paroxysmal AV block

testing who have higher APL values than normal subjects (Fig. 2).

Other relevant laboratory findings are as follows:

- Most patients with idiopathic AV block show a high susceptibility to the rapid IV injection of 18 mg adenosine or 20 mg adenosine triphosphate (ATP) test (Fig. 3). The adenosine/ATP test fairly reproduces spontaneous AV block. The adenosine response is abolished by theophylline, an adenosine antagonist, but not by atropine, a vagal antagonist.²
- Tilt table test may be positive, but positivity rate is lower than in patients with vasovagal syncope and is never able to reproduce an AV block. Thus tilt table test response seems to be nonspecific.
- Carotid sinus massage is almost invariably negative.

DIFFERENTIAL DIAGNOSIS FROM OTHER TYPES OF AV BLOCK

Idiopathic paroxysmal AV block has different clinical and electrophysiologic 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. Well-defined clinical and electrophysiologic features differentiate them.

Intrinsic paroxysmal AV block, which usually occurs in patients with underlying heart disease and/or abnormal standard ECG, is regarded as a manifestation of an intrinsic disease of the AV conduction system (Stokes-Adams attack), which is confirmed by abnormal electrophysiologic findings.^{3,4} The AV block is usually initiated by atrial, His, or ventricular premature extrasystole, increased heart rate (tachy-dependent AV block) or decreased heart rate (brady-dependent AV block), all features that support a diagnosis of intrinsic AV block (Fig. 4). The outcome is characterized by a rapid progression toward permanent AV block.^{3,4}

Extrinsic (vagal) AV block is localized within the AV node and is associated with slowing of the sinus rate. 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

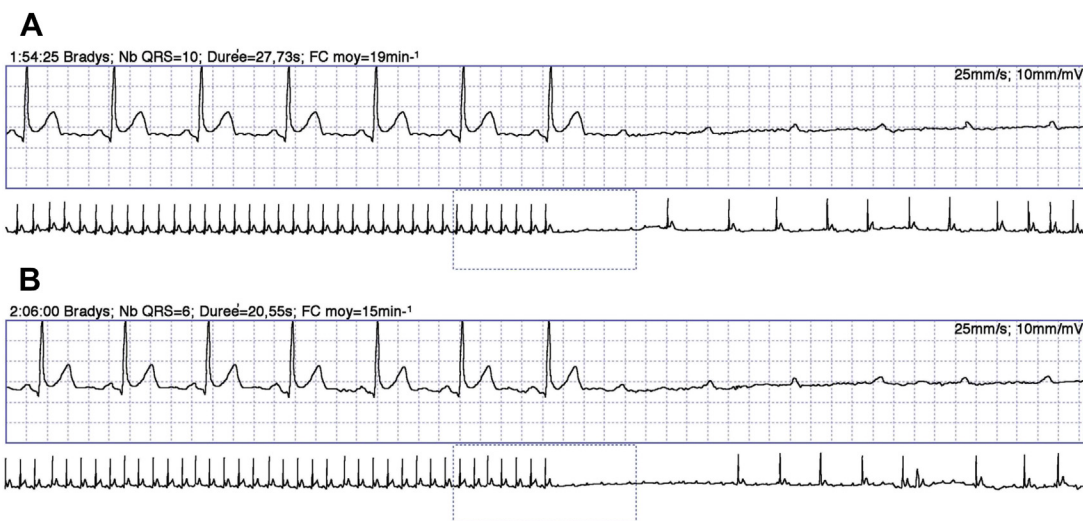


Fig. 1. Holter recording of 2 episodes of spontaneous syncope (A, B) that occurred a few minutes apart. The 2 episodes were very similar and were characterized by sudden-onset complete AV block without changes in P-P cycle length, which constantly remained 720 ms (top, trace), and long ventricular asystole of 7 and 11 seconds, respectively (bottom, compressed trace). (From Brignole M, Deharo JC, De Roy L, et al. Syncope due to idiopathic paroxysmal atrioventricular block. Long-term follow-up of a distinct form of atrioventricular block. J Am Coll Cardiol 2011;58:170; with permission.)

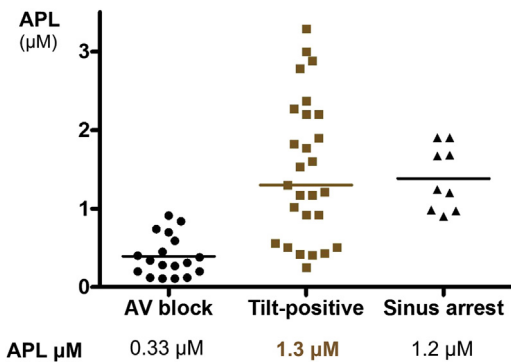


Fig. 2. The individual values of APL in 18 patients with idiopathic AV block patients, 9 patients with typical vasovagal syncope and documentation of sinus arrest during spontaneous syncope, and 27 patients with positive response during tilt table test. The horizontal line shows the median APL value of each group.

prominent AV response occurs, vagally mediated AV block is usually preceded by significant PR prolongation or Wenckebach; P-P interval prolongs markedly also during asystole and there is significant PR prolongation on resumption of AV conduction (**Fig. 5**).^{3,5-7} The patients affected by syncope caused by vagal AV block have different

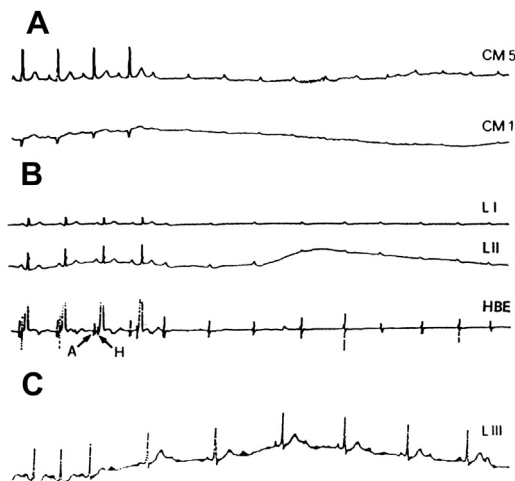


Fig. 3. (A) Ambulatory ECG monitoring. Normal heart rhythm is abruptly interrupted by paroxysmal AV block, which causes syncope. (B) ATP test. An IV bolus of 20 mg ATP reproduces syncope and spontaneous ECG pattern. His-bundle intracavitary recording (HBE) shows that P waves are blocked proximal to His-bundle deflection. (C) During oral theophylline therapy, ATP infusion causes asymptomatic 2:1 AVB without asystolic pauses. (From Brignole M, Gaggioli G, Menozzi C, et al. Adenosine-induced atrioventricular block in patients with unexplained syncope: the diagnostic value of ATP testing. *Circulation* 1997;96:3924; with permission.)

clinical features. Their episodes of syncope have well-identifiable triggers (central, ie, emotional distress, or peripheral, ie, prolonged standing) and are preceded by symptoms of autonomic activation (ie, feeling of warmth, an odd sensation in the abdomen, and lightheadedness or dizziness, nausea, and sweating).⁸ In addition, low APL values clearly differentiated idiopathic AV block patients from those with vasovagal syncope. High APL values seem to characterize vasovagal syncope and tilt-positive syncope (see **Fig. 2**). Thus, a different basal APL profile seems to be present in patients with idiopathic AV block and in patients with vasovagal syncope.⁹⁻¹¹ Finally, permanent cardiac pacing is successful in preventing syncopal recurrences during long-term follow-up in idiopathic AV block patients but much less effective 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.^{5,12} 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.

EPIDEMIOLOGY OF SYNCOPE DUE TO IDIOPATHIC AV BLOCK

Epidemiology of syncope due to idiopathic AV block is largely unknown because its diagnosis requires the (often fortuitous) ECG documentation of AV block at the time of syncope. The first description of adenosine-sensitive paroxysmal AV block was made by Brignole and colleagues² in 1997. The authors evaluated 15 syncope patients who had had the fortuitous ECG documentation of paroxysmal AV block. ATP testing showed an abnormal response in 6 of the 7 patients without structural heart disease and negative workup, whereas it was abnormal in only 2 of the 8 patients with associated abnormalities. The ECG of the ATP-sensitive patients showed the same characteristics of idiopathic AV block described above. Similar ECG features have been occasionally described in individual patients in clinical studies¹³ and in few case reports.¹⁴⁻¹⁷ The original description¹ included 18 cases.

In the absence of ECG documentation, syncope due to idiopathic AV block is undistinguishable from other forms of syncope without prodromes, which occur in patients with normal heart and normal ECG. Idiopathic AV block might be easily misdiagnosed as an atypical form of neutrally mediated syncope. Therefore, it is likely that its true prevalence is higher than that diagnosed. The prevalence of idiopathic AV block from ISSUE

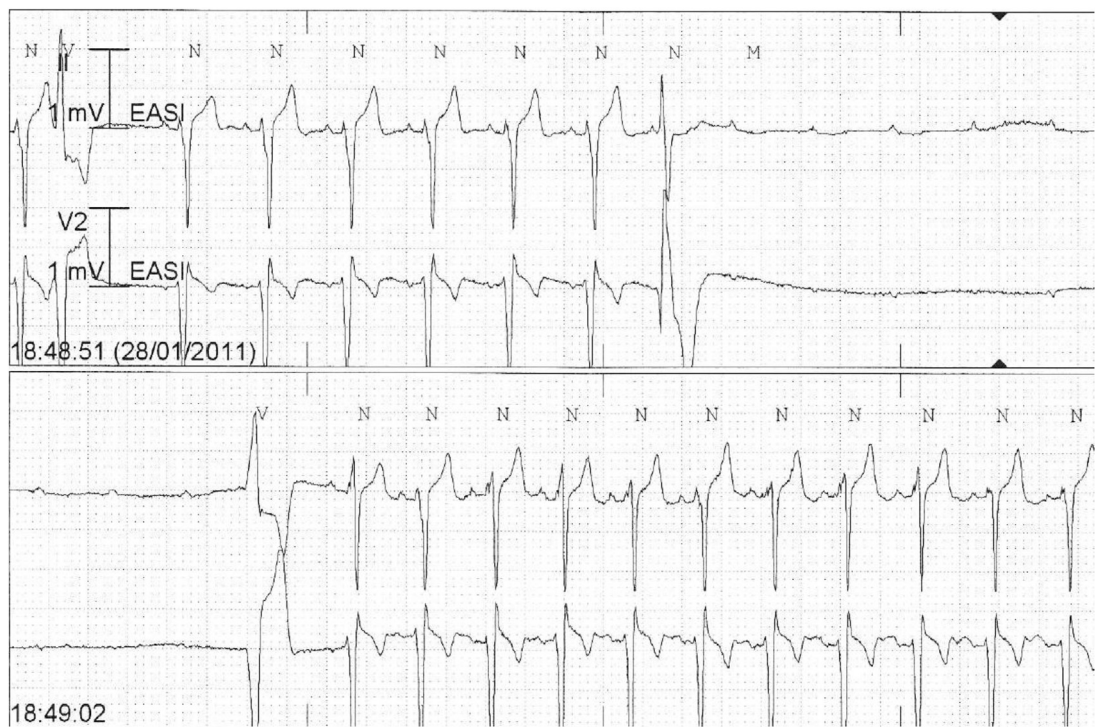


Fig. 4. Intrinsic paroxysmal AV block in a patient with underlying structural heart disease. The AV block was initiated by a ventricular premature extrasystole, and P-P cycle decreased during asystole due to activation of a compensatory reflex. The electrophysiologic study confirmed the site of the block below the His bundle (not shown in the figure).

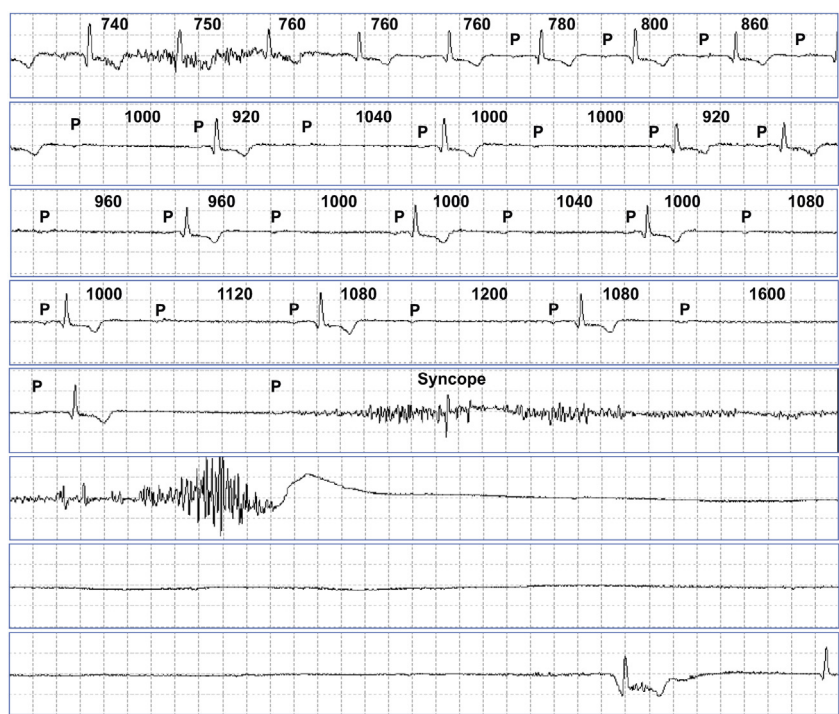


Fig. 5. Extrinsic (vagal) paroxysmal AV block documented by implantable loop recorder. A vagal mechanism is supported by the gradual slowing of the sinus rate (P-P interval) and AV conduction (prolonging PR and 2:1 block). During asystole AV block is replaced by sinus arrest. APL values in this patient were very high (1.9 μM), confirming the reflex nature of the episode.

2 and ISSUE 3 studies can be inferred.^{18,19} Type 1C form of the ISSUE classification⁶ of asystolic syncope resembles the ECG features of idiopathic AV block. In ISSUE 2 study,¹⁸ 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). In ISSUE 3 study,¹⁹ type 1C block was found to be present in 22% of those who had a diagnostic asystolic event. It can only be speculated 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 prevalence.

PATHOPHYSIOLOGICAL CONSIDERATIONS: THE PURINERGIC PROFILE AND THE ROLE OF ADENOSINE

The low observed baseline APL value (compared with controls and with patients with reflex asystolic syncope) and the rate of positive ATP test, which was much higher than that found in the literature in normal controls² and in patients with unexplained syncope,² indicate an increased susceptibility of the AV node to adenosine. These observations led to hypothesize some relationship between the adenosine pathway and the genesis of the AV block.

The effect of adenosine on different structures and organs involves activation of membrane receptor subtypes, named A_1 , A_{2A} , A_{2B} , or A_3 , depending on their primary sequence and affinity for ligands. The effect of adenosine on the AV node is mainly due to the stimulation of high-affinity A_1 receptors, which are much more numerous in the AV node than in the sinoatrial node.^{20–22} Like many other cell surface receptors, the number of cardiac adenosine A_1 receptors undergoes up-regulation and down-regulation when cardiac tissues are chronically exposed to low or elevated concentrations of adenosine receptor agonist (ie, adenosine). A transient release of endogenous adenosine could be sufficient to block conduction in the AV node when a high number of free high-affinity A_1 receptors in the AV node are available (low-APL patients). Conversely, when APL is high, as in patients with vasovagal syncope or positive tilt testing, most A_1 receptors in the AV node are saturated and AV block is unlikely to occur (Fig. 6). The cause of the transient release of endogenous adenosine responsible for paroxysmal AV block is unknown. Adenosine is a ubiquitous substance, which is released under several physiologic and pathologic conditions (eg, in

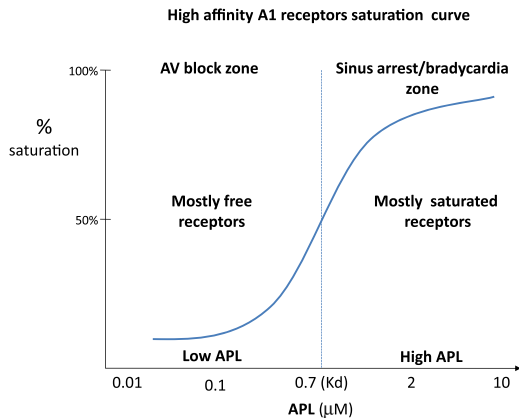


Fig. 6. Schematic description of the adenosine receptor-effector coupling system in the AV node, which is thought to have been responsible for paroxysmal AV block in the patients. The effect of adenosine on the AV node is mainly due to the stimulation of high-affinity adenosine A_1 receptors. Like many other cell surface receptors, the number of cardiac adenosine A_1 receptors undergoes up-regulation and down-regulation when cardiac tissues are chronically exposed to elevated concentrations of adenosine receptor agonist (ie, adenosine). The constant of dissociation (K_d) of A_1 adenosine receptors is 0.7 μ M. Around the K_d value, a high number of free high-affinity A_1 receptors in the AV node are available for activation. In this range, even a moderate increase in endogenous APL binds a high number of A_1 receptors, leading to AV block. Conversely, at high APL values, most A_1 receptors in the AV node are already saturated and endogenous adenosine is unlikely to cause AV block.

the case of myocardial hypoxia or during reflex β -adrenergic stimulation).^{23,24}

From a wider perspective, central or peripheral baroreceptor reflex abnormalities or alterations in neurohumoral mechanisms could play a pivotal role in the genesis of extrinsic (functional) and reflex syncope.²⁵ Despite differences in their receptors, adenosine and the neurotransmitter acetylcholine have remarkably similar effects on cardiac function.^{23,24,26,27} A possible explanation is the similarity of their receptor-effector coupling systems. In addition to having direct effects, acetylcholine and adenosine act synergistically against the stimulatory action of the sympathetic neurotransmitters noradrenaline and adrenaline on adenylyl cyclase. Thus, excitatory and inhibitory effects of the adrenergic cholinergic and purinergic outflows are integrated at the level of the receptor-effector coupling system, resulting in the final cardiac effect (Fig. 7).

In conclusion, even if a role of the adenosine pathway in the genesis of the AV block may be possible, the above data are insufficient to prove

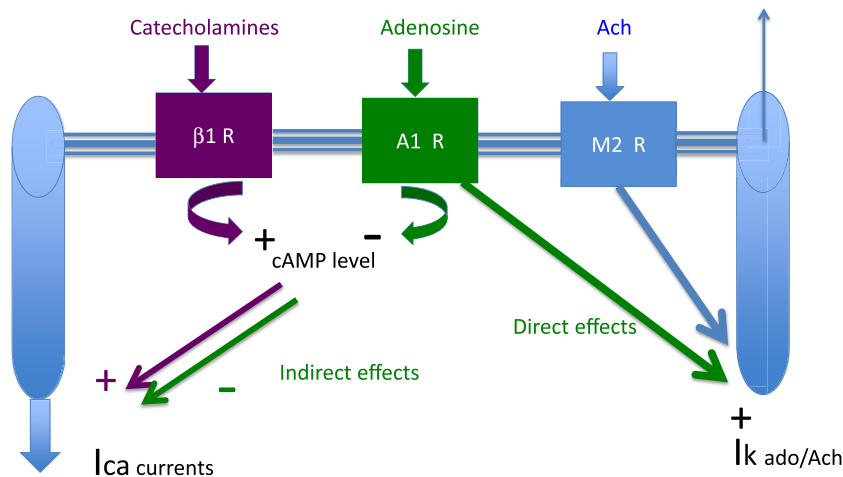


Fig. 7. The final effect of adenosine on heart rate is mediated by direct and indirect mechanisms. The indirect mechanism is the anti-adrenergic action of A1 adenosine receptors by opposing the effect of sympathetic nervous activation and β_1 stimulation by lowering intracellular cAMP levels in target cells.²⁶ The direct mechanism is due to the induction of a potassium current through an inward rectifier potassium channel, which leads to hyperpolarization of sinus node and AV node cells ($I_{K_{ado}}$).²⁷ This latter effect is very similar to that obtained with acetylcholine (ACh) on muscarinic receptors. β_1 R, β_1 adrenergic receptor; A1 R, A1 adenosine receptor; IK, inward going rectification; M2R, M2 muscarinic receptor.

a causality relationship. Therefore, the mechanism of the block in the patients remains largely unexplained (idiopathic AV block). The above observations might be of interest for the planning of future studies.

CLINICAL PERSPECTIVES

In clinical practice, patients with syncope who have the ECG documentation of paroxysmal AV block are usually regarded as a manifestation of an intrinsic disease of the AV conduction system and a diagnosis of cardiac syncope (primary arrhythmia) is made. Conversely, in the absence of ECG documentation, patients with unexplained syncope with normal heart would probably be categorized as affected by an atypical form of neurally mediated syncope. Therefore, 2 opposite diagnoses could be made in the same patient, depending on whether or not paroxysmal AV block during a spontaneous attack is documented on ECG.

In patients affected by unexplained syncope without prodromes, normal heart, and normal ECG, the diagnostic strategy usually calls for the early use of the implantable loop recorder (ILR). Most idiopathic AV block cases were identified by means of ILR. However, this strategy implies the implantation of a diagnostic device and the need of waiting until a relapse occurs. Is it possible to identify idiopathic AV block patients based on clinical features? The adenosine/ATP test seemed

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 ILR.^{11,12} The ability of APL value to discriminate idiopathic AV block cases from vasovagal syncope patients was evaluated using receiver operating characteristic curve analysis (Deharo JC et al, personal communication, 2013). A cutoff value of APL of ≤ 0.38 was found to have a sensitivity of 61% and a specificity of 92%. Applying to normal subjects without syncope, 22% of these had an APL value less than the cutoff value. The potential application in clinical practice of this cutoff requires further studies.

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