Adenosine hypersensitivity and atrioventricular block

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Adenosine, sometimes called the "retaliatory metabolite", is a ubiquitous substance that is released under several physiological and pathological conditions (e. g., in the case of myocardial hypoxia or during reflex β-adrenergic stimulation). The effects of adenosine on different structures and organs involves activation of membrane receptor subtypes, named A1, A2A, A2B, or A3, depending on their primary sequence and affinity for ligands. The main effects of adenosine on the cardiovascular system involve the activation of A1 and A2 receptors. The activation of A1 receptors mediates cardiac depression through negative chronotropic, dromotropic, and inotropic effects [1] and diminishes blood vessel tone. The effect of adenosine on the atrioventricular (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 [2]. The activation of A2A and A2B subtypes mediates artery relaxation [3, 4]. The affinity of these receptors for adenosine depends on the receptor subtype, the affinity of A1 receptors being superior to A2A receptors, which are superior to A2B receptors. Like many other cell surface receptors, the number of adenosine 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).

Role of adenosine in neurally mediated syncope

Several investigators have hypothesized that adenosine is an important modulator that can trigger vasovagal syncope in susceptible patients. From a diagnostic point of view, adenosine triphosphate injection, i. e. ATP testing, was proposed as a challenge in patients with syncope [5, 6]. Patients with syncope of unexplained origin have been shown to have an increased susceptibility to ATP testing compared with those without syncope [5]. ATP testing was also shown to be able to reproduce atrioventricular block (AVB) in patients with spontaneous paroxysmal AVB, especially in those without abnormalities of the AV conduction or autonomic nervous system [5]. Nevertheless, the value of ATP testing as a test for syncope remains controversial due to its low specificity, and its routine use has a low level of recommendation [7]. Saadjian et al. measured adenosine plasma levels (APLs) during head-up tilt testing in 26 patients that presented with unexplained syncope [8]. Patients with a negative head-up tilt test had baseline APLs that were in the same range as those reported in normal healthy volunteers. Patients with a positive tilt test had much higher baseline levels than did patients with a negative tilt test, with no overlap between the two groups. During syncope, APLs increased by an average of 52% compared with baseline levels. The higher the APL, the earlier the symptoms appeared and the greater the slowing of the heart rate. These observations suggest that adenosine release may be involved in the triggering mechanism of syncope induced during tilt testing. APL and A2A receptor (A2A R) expression were studied in patients with neurally mediated syncope [9]. In 46 consecutive patients with suspected neurally mediated syncope, APLs were measured and ATP and HUT tests were performed. High APL was associated with a high probability of positive HUT, while low APL was associated with a high probability of positive ATP. Expression of A2AR was lower in patients with positive ATP compared with those with positive HUT. These results suggest the presence of two distinct groups of patients with neurally mediated syncope: one with low APL and low A2AR expression and with positive ATP testing, and another with high APL, high A2AR expression, and positive HUT. Patients in the first group may be sensitive to the small increase in APL that occurs during ATP injection due to the activation of high affinity adenosine receptors (mostly A1R), leading to bradycardia. The patients from the second group are insensitive to ATP administration because most of their high affinity A1R may be desensitized by the chronic exposure to high APL. In addition, the small increase in APL that occurs after ATP administration is probably insufficient to activate lower affinity adenosine receptors (mostly A2A R); but these receptors are still activated during HUT as a result of the strong increase in APL that occurs during this test.

Translated into clinical practice, these observations can be interpreted as follows: in low-APL patients, a transient release of endogenous adenosine could be sufficient to block conduction in the AV node where a high number of free high-affinity A1 receptors are available; conversely, when APL is high, as in patients with vasovagal syncope or positive tilt testing, most A1 receptors in the AV node are saturated and AV block is un-

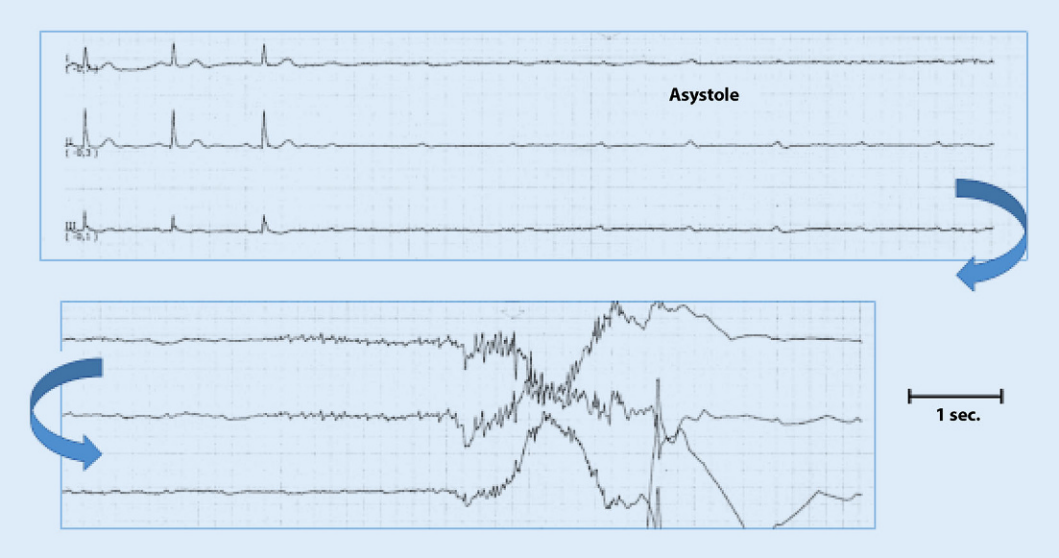

Fig. 1 ▲ ECG tracing recorded through in-bed telemetry monitoring during spontaneous syncope in a 72-year-old female. This patient was referred after five syncopal events that occurred in the 4 previous years. The patient never experienced prodromes and syncopal events resulted in severe trauma. She had a normal ECG and a normal electrophysiological study. ATP test was positive with a 6.3-s asystole due to atrioventricular (AV) block, and the head-up tilt test was positive, showing isolated vasodepression after nitroglycerin challenge. Adenosine plasma level (APL) was found to be extremely low (0.15 µMol/L). She received a pacemaker and never experienced syncope again over nearly 10 years of follow-up, during which she did not exhibit permanent conduction abnormalities. Note the sudden onset of prolonged asystole due to complete AV block with no change in PP intervals and no escape rhythm occurrence. Jerking movements during syncope are responsible for baseline oscillations

likely to occur, while vascular A2A R activation is responsible for vasodepression.

Low adenosine syndromes

Idiopathic AV block. A new clinical entity has recently been described in a small series of patients that presented with a long history of syncope and in whom paroxysmal AV block could be recorded at the time of syncope recurrence [10]. Similar observations have been reported by others [11]. **Fig. 1** shows a typical example of such a paroxysmal AV block episode. The term "idiopathic AV block" was used since these patients had an otherwise normal heart and no sign of conduction disease on ECG and electrophysiological study. No permanent AV block was seen at any time in these patients over very long periods of follow-up. A reflex mechanism involving adenosine was suspected in these patients with very low plasma adenosine levels and a high induction rate of transient complete heart block during exogenous injections of adenosine (i. e. during ATP testing). No syncope recurrence was observed after permanent cardiac pacing. The cause of the transient release of endogenous adenosine responsible for paroxysmal AV block is unknown. Idiopathic paroxysmal AV block is unique in the sense that it has different clinical and electrophysiological features from those of the two other known types of paroxysmal AV block: intrinsic AV block due to AV conduction disease and extrinsic vagal AV block. Well-defined clinical and electrophysiological features make them distinct (**Table 1**). 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, which is confirmed by abnormal electrophysiological findings [12]. 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. The outcome is characterized by a rapid progression toward permanent AV block. Extrinsic vagal AV block is localized within the AV node and is associated with slowing of the sinus rate [13]. 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 two conditions frequently coexist, indicating a simultaneous vagal action on the 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 Mobitz 1 periods; the P-P interval also prolongs markedly during asystole and there is significant PR prolongation on resumption of AV conduction. The patients affected by syncope caused by vagal AV block have different clinical features [7]. Their episodes of syncope have well-identifiable triggers and are preceded by symptoms of autonomic activation. In addition, low APL values clearly differentiate idiopathic AV block patients from those with vasovagal syncope. High APL values seem to characterize vasovagal syncope and tilt-positive syncope. Thus, a different basal APL profile seems to be present in patients with idiopathic AV block and in patients with vasovagal syncope. Finally, permanent cardiac pacing is successful in preventing syncopal recurrences dur-

ing long-term follow-up in idiopathic AV block patients, but much less effective in patients affected by vasovagal cardioinhibitory syncope, even if a spontaneous asystolic reflex has been documented, with syncope recurring in 9%–45% of patients. 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.

Low adenosine syncope. Low adenosine syncope is an entity which has recently been described and enlarges the spectrum of idiopathic paroxysmal AV block. Patients that have otherwise unexplained syncope with sudden onset (i. e., without or with very short prodromes) and a normal heart and normal electrocardiogram [14] were shown to exhibit clinical, laboratory, and biological features that are very close to those observed in patients affected by idiopathic paroxysmal AV block. Unlike in vasovagal syncope patients, tilt testing is usually negative [14, 15]. No syncope recurrence was observed after permanent cardiac pacing in 10 patients that had ECG documentation of asystolic pause due to sinus arrest or AV block [16]. The features distinguishing "low adenosine syncope" from vasovagal syncope are summarized in **Table 2**.

Adenosine levels and clinical forms of neurocardiogenic syncope

The purinergic profile of four common forms of syncope has recently been evaluated: typical vasovagal syncope; situational syncope; carotid sinus syncope (CSS); and syncope without prodrome or with very short (2–3 s) prodromes and a normal heart [15]. The purinergic profile evaluation included baseline APL and characterization of A2A R expression and single nucleotide c.1083 C > T polymorphism (SNP), which is the most common SNP in the A2A R gene. Clinical and biological characteristics of patients and control subjects were compared. Compared to control subjects, no-prodrome and CSS patients had significantly lower APLs, while vasovagal patients had significantly higher APLs and situational syncope patients had comparable APLs. Compared to controls, A2A R expression was higher in vasovagal and situational syncope patients and lower in no-prodrome patients. These findings demonstrate an association between APLs and unexplained syncope in patients without prodromes, CSS, and VVS that have profiles different from normal control subjects. Conversely, adenosine is not associated with situational syncope, which is mainly triggered by well identifiable afferent neural reflexes. These results were partly confirmed in a prospective multicenter study in which 58 patients presenting with unexplained syncope, no prodromes, and a normal heart received an implantable loop recorder (ILR) and were followed up until a diagnosis was established [16]. During an observation period of 16 ± 13 months, a diagnostic event was documented by the ILR in 29 patients. An asystolic pause of 11 ± 5 s (range 3.5–22 s) was present at the time of the diagnostic event in 19 patients. These outcomes were compared with those of 389 patients affected by reflex syncope with prodromes who received an ILR. Compared with patients affected by reflex syncope with prodromes, pa-

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Abstract

Adenosine is a ubiquitous substance that is released under several physiological and pathological conditions and has cardiovascular effects including cardioinhibition and vasodilation. It has been shown to be an important modulator implicated in several forms of syncope. In patients with chronic low plasma levels of adenosine, a transient release of endogenous adenosine can be sufficient to block conduction in the atrioventricular node and induce prolonged asystole; conversely, when plasma adenosine levels are chronically high, adenosine release is responsible for vasodepression. Distinct purinergic profiles in patients presenting with syncope have recently been correlated with the clinical presentation: "low-adenosine patients," prone to asystole, may present with idiopathic atrioventricular block, carotid sinus syndrome, or syncope with no or very brief prodromes and normal heart; "high-adenosine patients," prone to vasodilation, experience vasovagal syncope. This pathophysiological classification may have therapeutic implications.

Keywords

Syncope · Atrioventricular node · Hypotension · Purinergic · Asystole

Adenosinhypersensitivität und atrioventrikulärer Block

Zusammenfassung

Adenosin ist eine allgemein vorkommende Verbindung, die unter vielen physiologischen wie auch pathologischen Bedingungen freigesetzt wird und kardiovaskuläre Effekte hat, unter anderem auch kardioinhibitorische und vasodilatatorische. Es ist belegt, dass Adenosin als wichtiger Modulator in Bezug auf verschiedene Synkopeformen fungiert. Bei Patienten mit chronisch niedrigen Adenosinplasmaspiegeln kann eine transiente Freisetzung von endogenem Adenosin ausreichend sein, um die Erregungsleitung im atrioventrikulären (AV) Knoten zu blockieren und eine anhaltende Asystolie hervorzurufen. Umgekehrt hat die Adenosinfreisetzung bei chronisch hohen Plasmaspiegeln eine vasodepressorische Wirkung. Unterschiedliche purinerge Profile von Patienten mit Synkope sind in jüngerer Zeit mit dem klinischen Bild in Beziehung gebracht worden: Patienten mit niedrigem Adenosinspiegel neigen zu Asystolie und können einen idiopathischen AV-Block, ein Karotissinussyndrom oder eine Synkope ohne oder mit sehr kurzen Prodromen und normalem Herzen aufweisen; Patienten mit hohem Adenosinspiegel neigen zu Vasodilatation und zeigen vasovagale Synkopen. Diese pathophysiologische Klassifikation könnte von therapeutischer Relevanz sein.

Schlüsselwörter

Synkope · Atrioventrilulärknoten · Hypotonie · Purinerg · Asystolie

Table 1 Features distinguishing different types of paroxysmal AV block

	Intrinsic	Extrinsic	
		Vagal	Idiopathic AVB
Level	Below AV node	AV node	AV node
Mechanism	Diseased tissue	Vagal tone	Adenosine release (A1R activation)
Baseline ECG	Abnormal	Normal	Normal
Initiated by premature beat	Yes	No	No
Tachycardia before AVB	Possible	No	No
Initiation			
PP lengthening	Possible	Yes	No/modest
PR prolongation	No	Yes	No/modest
Resumption of conduction	Appropriately timed beat	Vagal input withdrawal Sinus rate acceleration	Spontaneous? Modest sinus rate acceleration

AV atrioventricular, *AVB* atrioventricular block

Table 2 Features distinguishing low adenosine syncope from vasovagal syncope

	Low adenosine syncope	Typical vasovagal syncope
Age	Older patients (typically over 50 years)	Younger patients
Number of previous syncope	Typically low	Variable—May be high
Duration of syncopal spells	Shorter (few years)	Longer
Trauma due to syncope	Frequent	Rare
Prodromes	Absent or very short	Longer
Head-up tilt test	May be negative	Frequently positive
ATP test	Frequently positive	May be negative
Adenosine plasmatic level	Low (<0.35 µmol/l)	High (>0.7 µmol/l)
Electrocardiographic documentation of syncope	Asystole due to atrioventricular block much more frequently than to sinus arrest	Sinus bradycardia or sinus arrest more frequent than atrioventricular block
In case of atrioventricular block documentation during syncope	Sudden onset, i. e. with no or very slight changes in PP intervals before, during and after the episode, without escape rhythm	Preceded by PP interval lengthening (or, less commonly shortening), with PP prolongation during the atrioventricular block episode, with sinus acceleration at the time of resumption of conduction
Cardiac pacing	Highly effective	Effective only when asystole (mainly sinus arrest) is documented at the time of syncope

tients with unexplained syncope, no prodromes, and a normal heart more frequently had asystolic syncope (66% vs 47%; $P = 0.001$), and this was more frequently due to idiopathic paroxysmal atrioventricular block (47% vs 21%; $P = 0.04$). A total of 10 patients with asystolic pauses underwent cardiac pacing, and eight patients underwent oral theophylline treatment. During the subsequent 17 ± 12 months of follow-up, syncope recurred in one patient on theophylline, and presyncope occurred in one patient with pacemaker.

Conclusion

The evaluation of the purinergic profile of patients with syncope may help to distinguish different forms and, in turn, select the appropriate therapy: low-APL patients, prone to asystole, including idiopathic AV block, carotid sinus syndrome and syncope with no or very brief prodromes and normal heart; and high APL patients, prone to vasodilation, being vasovagal patients.

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Compliance with ethical guidelines

Conflict of interest. J.-C. Deharo, M. Brignole and R. Guieu declare that they have no competing interests.

This article does not contain any studies with human participants or animals performed by any of the authors.

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