Is There Any Room for Adenosine Test in Syncope of Unknown Origin?

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SUMMARY

Background

Some patients with unexplained syncope develop different degrees of paroxysmal AV block with bolus infusion of 18-mg of adenosine. This finding had a low positive predictive value in recent trials, although its use was not standardized.

Objective

To present the experience in our institution in follow up of patients with a first episode of unexplained malignant syncope of uncertain etiology (SUE), to whom were systematically carried out an adenosine test.

Material and Methods

There were included, in a prospective and consecutive way, patients who presented unexplained syncope with severe trauma, none of them had a previous history of syncope, without suspected vasovagal etiology, without organic cardiopathy, with normal neurological and cardiological studies (including sensitized tilt test), to those who underwent an adenosine test. The test was carried out at the end of the electrophysiological study. It was infused in bolus of 18-mg of adenosine through the femoral vein under continuous ECG monitoring; positive test was defined by the development of complete AV block with pauses longer than 6 seconds.

Results

Between 1999 and 2009 adenosine test underwent to 29 patients (mean age 63 ± 12 years, 17 women). The test was positive in 17 patients, with a mean pause of 10,185 ± 3,430 msec. The mean age in this group was 64 ± 13 years, 13 were women. In the remaining 12 patients (59 ± 11 years), the test was negative, with a mean pause of 2,570 ± 1,067 msec. All patients received hygienic-dietetic recommendations for the prevention of neurally mediated syncope and 9 patients with positive adenosine test, a permanent pacemaker was implanted. The follow-up was 51 ± 37 months. Only 2 patients had recurrence of syncope, both with positive adenosine test without pacemaker implantation.

Conclusions

Patients with syncope of uncertain etiology and high initial risk represent in monitoring a low clinical risk population with a very low recurrence rate, regardless of the implemented therapeutic strategy.

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Key words > Syncope - Adenosine – Cardiopathies

Abbreviations >

ATP	Adenosine Triphosphate	**EPS**	Electrophysiological Study
AV	Atrioventricular	**SUE**	Syncope of Uncertain Etiology
ECG	Electrocardiogram	**TT**	Tilt test

BACKGROUND

Although progress has been made in diagnosis and treatment of syncope, up to 30% to 40% of patients remain undiagnosed after initial assessment, even with the carrying out of a tilt test.

In the late nineties, Flammang and afterwards Brignole showed that certain patients with syncope of uncertain etiology (SUE) are susceptible to bolus infusion of 20 mg of adenosine triphosphate (ATP),

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with different degrees of development of paroxysmal atrioventricular block (AV). (1, 2) Recent studies demonstrated a low positive predictive value of the test, although their implementation was not standardized.

With this study we present our experience in the follow up of patients with a first episode of malignant SUE to whom were systematically carried out an adenosine test.

MATERIAL AND METHODS

There were included, in a prospective and consecutive way, patients older than 40 years with malignant SUE that required hospitalization. Malignant syncope was defined to that which occurred with severe facial trauma. All patients underwent a thorough clinical examination and they were excluded patients with previous history of syncope, neurological or cardiac history, and those with stigmas which make to suspect a vasovagal origin. In all cases was carried out ECG, Holter, echocardiography, brain computed tomography, sensitized tilt test with isosorbide dinitrate and neurological assessment.

We excluded all patients that showed some degree of cardiopathy or abnormal ECG by any criteria. Thus, only those with normal studies were referred to the hemodynamic room to carry out an electrophysiology study (EPS) and a test of adenosine.

Protocol of Electrophysiological Study and Adenosine Test

The EPS was carried out, prior signature of an informed consent, by right femoral puncture, two electrode catheters were introduced for record and stimulation. In all the cases underwent programmed atrial stimulation and programmed ventricular stimulation with two extrastimuli after registration of the conduction intervals at level of the bundle of His. In patients older than 50 years it was carried out bilateral carotid sinus massage prior exclusion of the presence of heart murmur at that level. In patients with normal EPS proceeded to bolus infusion of 18-mg of adenosine with continuous ECG recording. The test was considered positive only if a ventricular pause greater than 360 msec was obtained.

Behaviour to take after adenosine test was left to the judgment of the treating physician, the family physician and the patient's desire, taking into account its controversial interpretation.

In this remark we propose to evaluate the prevalence of positive adenosine test in this so selected population, demographic variables of patients with positive and negative test and the impact on the clinical progress of the strategy of pacemaker implantation in patients with a positive result.

RESULTS

Over 10 years of evaluation, only 29 patients fulfilled the inclusion criteria. The mean age was 63 ± 12 years and 17 were women.

The test was positive in 17 patients. The mean age was 64 ± 13 years. Thirteen were women (76%). The mean pause was 10,185 ± 3,430 msec. Three patients reproduced syncope during the study and the rest had presyncopal symptoms (Figure 1).

In the remaining 12 patients the test result was negative. Their mean age was 59 ± 11 years and the mean pause was 2,570 ± 1,067 msec (Figure 2).

All patients received hygienic-dietetic recommendations for the prevention of neurally mediated syncope.

Patients with positive adenosine test were suggested the possibility of carrying out the implantation of a permanent pacemaker, emphasizing the limited medical knowledge about the clinical implications. Nine patients agreeded to implant a dual chamber permanent pacemaker. The 9 patients were female and the mean pause was 11,491 ± 4,100 msec. In all cases the pacemaker was programmed in VVI mode at 40 bpm to promote their own pace. In the 8 patients who did not received a pacemaker, the mean pause was 8,808 ± 2,199 msec.

The follow-up was 51 ± 37 months. During this time all patients were evaluated in doctor's office or by telephone. No no patient was lost at follow up. Only 2 patients had recurrence of syncope, both with positive

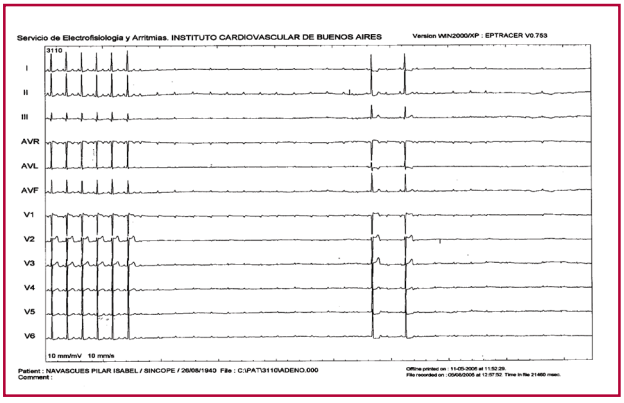

Fig 1. Positive adenosine test. Note the presence of paroxysmal AV block with a pause of 12 sec followed by a secondary pause of 10 sec. The patient had convulsive syncope during the test.

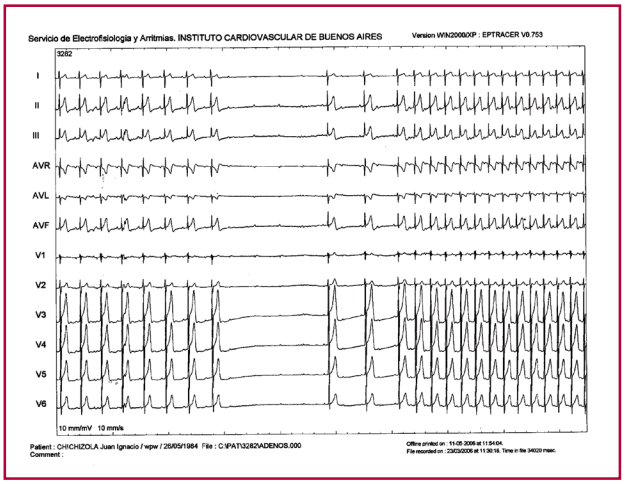

Fig 1. Negative adenosine test. Note the presence of paraxysmal AV block with a pause of 2.3 sec.

adenosine test without pacemaker implantation. These patients had presented a pause during the adenosine test of 14,000 and 9,000 msec, unlike those who did not suffer a recurrence, which showed mean pause 8,213 ± 1,125 msec (Table 1). Both cases had a single episode without clinical consequences. A new sensitized TT was negative. In one of them was implanted a monitor of events. At follow-up of the group with permanent pacemaker, the pacing rate (according to the history of the device) was less than 1%.

DISCUSSION

Classically, it was defined SUE to syncope that remains undiagnosed after a thorough clinical examination, an electrocardiogram and some positive study. Before the introduction of the TT as a routine method, the percentage of syncope of uncertain etiology increased to 35%. With the advent of TT it was observed that up to 50% to 60% of these patients were susceptible to the development of neurocardiogenic syncope. Subsequently, the use of monitor of implantable events allowed to confirm the etiologic diagnosis in 30% of patients with SUE, with bradyarrhythmias as the predominant cause. (3) However, this last strategy was useful only in patients with recurrent syncope. (4)

In the early years of this decade, French and Italian authors showed that some patients with SUE have a particular susceptibility to the intravenous injection of adenosine triphosphate, which by its negative dromotropic effect on AV node produces sequences of paroxysmal AV block, which could correlate to the cause of syncope. The protocol involved the injection of 20 mg of ATP dissolved in 10 ml saline bolus. Flammang considered that the test was positive when a pause of 10 seconds was produced by paroxysmal AV block, or sinoatrial block regardless of the presence or absence of escape beats. Moreover, Brignole defined positive test for the presence of more than 6 seconds of ventricular asystole. Following these protocols, the incidence of positive test in SUE was 28% to 41%, with an incidence of false positives by only 5%. The reproducibility of the positive test was 80%. (5)

Several authors suggested that adenosine could be a modulator of vasovagal response; (6) however, positive adenosine patients show some clinical differences with positive TT patients. In positive adenosine patients, syncope usually occurs for the first time in middle or advanced ages of life, in general with little or null prodromes and in situations not clearly predispose to a vasovagal reaction. However, up to a quarter of patients with positive TT have positive adenosine test and 15% of patients with clear neurocardiogenic syncope have evidence of positive adenosine. This suggests that in this population without organic cardiopaphy the mechanisms of syncope may be manifold. (7)

Table 2. Results

	Adenosine (+) (n = 17)	Adenosine (–) (n = 12)
Age, years	64 ± 13	59 ± 11
Female, n	13	4
Male, n	4	8
Mean pause, msec	10,185 ± 3,430	2,570 ± 1,067
Implant of pacemarker, n	9	0
Recurrence of syncope, n	2	0

From 2003 a series of studies were published that were relegated the clinical utility of adenosine test. In the first, Donateo and et al. evaluated patients older than 40 years with recurrent syncope, without structural cardiopathy and positive adenosine test, to whom a monitor of events was implanted. At follow up, 16 patients had recurrence of syncope, of which 8 patientes had positive TT and 8 patients had negative TT. In the first group, 5 patients had sinusal pauses and 2 patients had sinusal bradycardia, unlike the second group, in which 3 patients presented a paroxysmal AV block and, one had sinusal arrest. (8, 9)

The greatest clinical experience with the adenosine test was published by Flammang et al. (10) Over a total of 316 patients (mean age 74 years) with syncope or presyncope of uncertain etiology, the test was positive in 130 patients (41%). A median follow up of 50 months, recurrence in the group with positive adenosine test was 13.5% when pacemakers were implanted, against 48% when they did not receive PM ($p < 0.0001$). In the group with negative adenosine test, the recurrence was 15% and 21%, regardless of having been carried out or not the implantation of a pacemaker. Later, in 2006, the study ISSUE 2 was presented (11) which included 392 patients with SUE and without structural cardiopathy whom were implanted with a monitor of events. Adenosine test and TT were recommended, but their implementation was left to the treating physician's discretion. Anyway, in 343 patients underwent a TT that was positive in 48% of cases and in 182 patients it was carried out an adenosine test which was positive in 30%. At follow-up of 12 ± 8 months, 36% had recurrence of syncope. There was little correlation between adenosine test results and the mechanism of syncope. Only 8 of 14 patients with positive adenosine test showed asystole at the time of recurrence and 18 of 38 patients with negative test also showed asystole in recurrence. However, negative TT and positive adenosine patients were not analyzed. In 2006, Perennes and et al. (12) assessed a population of 137 patients with SUE and negative TT. Only 9 patients had a positive result of adenosine test (6.6%). At follow-up of 31 ± 14 months, only 2 patients suffered a recurrence of syncope.

With these results, different authors adopted a critical attitude with regarding to adenosine test and on the basis of these contradictive results, and the benign nature of the syndrome, adenosine test was considered class II by the European Task Force and its recent update passed it to class III. (13-15)

In our clinical experience, a very specific population was considered: patients of middle or advanced age who presented severe, traumatic syncope, without typical predisposing situation and without vasovagal stigmas, in whom all diagnostic studies were negative, including the sensitized TT with dinitrate sublingual isosorbide and the EPS. In this so selected population, the incidence of positive adenosine test was 58%. This positivity is higher than the previously published, which was 28% and 41%, which may be related to the careful selection of the population. As in other publications, women were more likely to a positive result and mean age was also higher than in those with positive adenosine test.

The first interesting observation was that in this population, initially considered of high risk, clinical outcome was excellent, especially in patients with negative adenosine test. In this subgroup there were no recurrences. In those patients with positive adenosine test, recurrence was null when a pacemaker was implanted to them. The only two recurrences were observed in patients with positive test and without pacemakers. This differs from what was published by other studies, in which the recurrence of syncope was similar in patients with positive and negative adenosine test and in which bradycardia was the main finding in both groups. However, the population in these studies was different. The included patients had recurrent unexplained syncope and absence of organic cardiopathy, but neurocardiogenic syncope was not systematically excluded. In patients with positive adenosine test there were no recurrences of syncope when a pacemaker was implanted The recurrence was 25% in those with positive adenosine test that were not treated with permanent pacemaker. These findings imitate the clinical experience of Flammang et al., where the higher recurrence rate was limited to the group with positive adenosine test and without pacemaker. However, our study was not randomized and the recurrence rate was very low, making it difficult to draw definitive conclusions.

Following the European Task Force, recently updated, a first event of syncope without organic cardiopathy could not continue in study aside from that the syncope is considered high risk. In our population is difficult not to carry out with the etiologic diagnosis and not to recommend the appropriate treatment because of the natural demand of security by patients and their families. Implantation of a monitor of events could be of little use taking into account the very low rate of recurrence and it is here where the adenosine test could have a precise indication.

CONCLUSIONS

Patients with syncope of uncertain etiology and initial high risk present at follow up a population of low clinical risk, with very low recurrence rate, especially when the test is negative adenosine. However, given the low incidence of clinical events it was impossible for us to evaluate the positive predictive value of the test. Adenosine test could be useful in this so particular population, which starts with syncope in an advanced age of life, without organic cardiopathy and without vasovagal stigmas. New studies that include a larger population and a prospective, randomized design could be useful to confirm this observation.

RESUMEN

Prueba de adenosina en el síncope de origen desconocido: ¿queda algún espacio para su indicación?

Introducción
Algunos pacientes con síncope inexplicado desarrollan distintos grados de bloqueo AV paroxístico con la infusión en bolo de 18 mg de adenosina. Este hallazgo tuvo un valor predictivo positivo bajo en ensayos recientes, aunque su utilización no estuvo normatizada.

Objetivo
Presentar la experiencia en nuestra institución en el seguimiento de pacientes con un primer episodio de síncope de origen desconocido (SOD) maligno, a quienes se les realizó sistemáticamente una prueba de adenosina.

Material y métodos
Se incluyeron en forma prospectiva y consecutiva pacientes que presentaban síncope inexplicado con traumatismo grave, sin antecedentes sincopales previos, sin sospecha de etiología vagal, sin cardiopatía orgánica, con estudios neurológicos y cardiológicos normales (incluido tilt test sensibilizado), a los que se les realizó una prueba de adenosina. La prueba se efectuó al final del estudio electrofisiológico. Se infundieron en bolo 18 mg de adenosina por la vena femoral bajo monitorización electrocardiográfica continua; se definió prueba positiva al desarrollo de bloqueo AV completo con pausa mayor de 6 segundos.

Resultados
Entre 1999 y 2009 se les realizó una prueba de adenosina a 29 pacientes (edad promedio 63 ± 12 años, 17 mujeres). La prueba fue positiva en 17, con una pausa promedio de 10.185 ± 3.430 mseg. La edad promedio de este grupo fue de 64 ± 13 años, 13 eran mujeres. En los 12 pacientes restantes (59 ± 11 años), la prueba fue negativa, con una pausa promedio de 2.570 ± 1.067 mseg. Todos recibieron recomendaciones higiénico-dietéticas para la prevención del síncope neuromediado y en 9 pacientes con prueba de adenosina positiva se implantó un marcapasos definitivo. El seguimiento fue de 51 ± 37 meses. Sólo 2 pacientes tuvieron recurrencia del síncope, ambos con prueba de adenosina positiva y sin implante de marcapasos.

Conclusiones
Los pacientes con síncope de origen desconocido y riesgo inicial alto representan en el seguimiento una población de riesgo clínico bajo, con una tasa de recurrencia muy baja, independientemente de la estrategia terapéutica implementada.

Palabras clave > Síncope - Adenosina - Cardiopatías

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