

Role of Adenosine Test in Syncope of Unknown Origin

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Adenosine is an endogenous purine nucleotide that modulates various physiological functions. Rapid intravenous administration has a short effect, given its rapid metabolism. Initially sinus bradycardia is observed, with or without AV block, followed by a period of sinus tachycardia. (1) Some studies also showed activation of excitatory cardiac afferent fibers. (2) Given these findings, the drug was used to investigate the mechanisms of vasovagal syncope and in 1996, Shen et al. described the adenosine as a potential modulator in vasovagal syncope. (3) In 1997, Flammang and et al. used ATP in patients with recurrent syncope of uncertain etiology (SUE). The rate of test positivity (pause > 10 sec) was 41%. To these patients were recommended a pacemaker and the rate of recurrence in patients with pacemaker was significantly lower compared with patients without this device. This means that the use of ATP could identify a population at risk of severe cardioinhibitory response. (4) In the same year, Brignole et al. carried out a similar study. The rate of an abnormal response to ATP (pause > 6 sec) was 28%. At follow up, some patients had recurrence of syncope with ECG register of AV block and, in retrospect, 84% of this population had had an abnormal test of ATP. The study concluded that some patients with SUE had an ATP hypersensitivity manifested by the development of AV block, which offered the possibility to use the test to identify patients with syncope of probable bradyarrhythmic etiology (5).

Unfortunately, these findings were not confirmed in subsequent studies. Donateo and et al. used APT in patients with SUE and in those with a positive test (pause > 6 sec) implemented an event-recorder. At follow-up, half of the patients had recurrences but with different recorded rhythms in addition to bradycardia, that is to say, that the mechanism of syncope in this population appears to be heterogeneous. (6) Moreover, the study ISSUE-2 (The International Study of Syncope of Uncertain Etiology) group introduced a recorder of events in patients with severe recurrent syncope with probable vasovagal etiology. The ATP test was positive (pause > 6 sec) in 29% of patients. At follow up, the presence of syncope was not related to the outcome of the ATP test. The authors concluded that the ATP test has no value to predict therapies. (7)

In the present issue of the Journal, Albina and et al. report their experience in the use of adenosine in patients with malignant SUE. (8) The study included patients over 40 years, with a first episode of malignant syncope (presence of severe facial trauma) requiring hospitalization. Patients with previous syncopal events were excluded, as well as, patients with cardiopathy,

abnormal ECG or with vasovagal stigmas. There was no control group. At the end of 10 years, 29 patients were included and tested for adenosine (which has the same effects as ATP, but it is more stable at room temperature). The test was positive (pause > 6 sec) in 17 (59%) patients, 9 (53%) of whom received a pacemaker. At follow up, a little over 4 years, only two patients (adenosine positives and without pacemaker) had syncope. The authors conclude that these patients with a first episode of malignant SUE, represent in monitoring a population of low clinical risk, with a low rate of recurrence, especially when the test of adenosine is negative. They also suggest that adenosine test may be useful in this population.

This study is of great importance, as it shows a follow up for more than 4 years in a population without cardiopathy, vasovagal featureless, with a first syncopal event associated with facial trauma, which has a very low rate of recurrence, regardless of used therapy. This is the fundamental message of the study. Some points in this study deserve attention. First, the authors recognize the selected characteristics of the population: patients with first episode of malignant syncope with a negative work-up. The enrollment rate was low, less than 3 patients per year. However, the authors were persistent in continuing the monitoring of patients enrolled early in the study. There were no lost patients to follow-up. Malignancy of the syncope was given by the presence of severe facial trauma. Thus, patients with other injuries were eliminated, such as hip fracture or with damage associated with the episode, such as traffic accidents (features that also give character of malignancy). The fact to include patients with first syncopal episode has a huge importance, since the number of episodes of syncope during the patient's life is the most important variable of prediction of recurrence. For patients over 40 years, with one or two full episodes of syncope undiagnosed and low risk, the rate of recurrence is 20% in two years, three syncopal episodes increase the rate of recurrence to 42%. (9) Choosing a population with the first syncopal event, the authors selected a population with a low rate of recurrence. This is one of the reasons why syncope guidelines recommend that once determined that the patient is low risk, with a single benign syncopal episode, it is considered no further studies. (10) For patients like those included in Albina and et al.'s study, the risk derives from syncope morbidity, the trauma associated with the event, and there arises the need to reach a diagnosis. The authors add, with good base, that the implant of an event recorder is probably not useful given the low frequency of recurrence. Likewise, they suggest that perhaps the

adenosine test may be used in this instance. From the present study is not clear the usefulness of the test in this population. The rate of recurrence was low in the total group without regarding prescribed therapy or the result of the test. The numbers of recurrences are low in the different groups for any statistical inference, without considering the follow-up time in each of them.

Following the article title, "Adenosine Test in Syncope of Uncertain Etiology: is there still any space for its indication?", according to the study, this population does not seem useful. The rate of recurrence is very low regardless of the outcome of the test or therapy. What is the future of the test? A recent work that studied patients with indication of pacemaker showed that the test was positive in 100% of these cases. (11) Now, these patients are already in the late stage of the disease, the problem lies in applying this test early in order to identify those patients who later in life may need a pacemaker. We should consider that we do not know how to use this test. In future studies would be important to include as therapy in patients hypersensitive not only pacemaker, but also direct inhibitors of adenosine as xanthines, which have demonstrated in small uncontrolled trials to be effective in these patients. (5)

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