The role of adenosine in neurogenic syncope: much ado about something?

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Neurogenic or vasovagal syncope remains an important societal problem. It is the cause of substantial disability, often in otherwise healthy individuals. The diagnostic work-up of patients with syncope continues to consume vast resources but the cause of syncope cannot be determined in a significant proportion of patients. Treatment remains a challenge and is often ineffective. These shortcomings in the management of neurogenic syncope may reflect our lack of understanding of the underlying pathophysiology. It is well established that once this abnormal reflex is triggered, it elicits sudden sympathetic withdrawal and vagal activation, with either a predominant cardioinhibitory (bradycardia), vasodepressor (profound hypotension with only mild bradycardia), or mixed patterns. In contrast, the mechanisms responsible for the triggering of this abnormal reflex are in dispute. The most frequently mentioned mechanism is sympathetic activation that precedes the activation of cardiac mechanoreceptors or chemoreceptors. Neurogenic syncope, however, can be induced in patients with denervated hearts because of cardiac transplantation, implying that afferents outside the heart may also be involved. Also, recent studies [1] have raised doubts about the role of the initial sympathetic activation in the genesis of posture-related neurogenic syncope.

Several chemical signals, including adenosine, have been implicated in the triggering of this abnormal reflex. There is indirect evidence supporting this hypothesis. First, the adenosine receptor antagonist theophylline has been reported to reduce syncopal episodes [2], particularly in young patients with bradyarrhythmias [3]. These results would suggest that endogenous adenosine was contributing to syncope, but these studies were not placebo-controlled. Second, syncope and bradycardia are among the side effects of clinically used dipyridamole. Dipyridamole blocks the cellular uptake of adenosine, thereby raising its interstitial concentrations. It is possible, therefore, that the side effects of dipyridamole represent the actions of endogenous adenosine. Third, exogenous adenosine induces bradycardia and may trigger vasovagal reactions, particularly in syncope patients. When given as a rapid bolus injection at relatively high doses (about 150 μg/kg or 12 mg) to syncope patients during upright tilt, adenosine produced the expected biphasic changes in heart rate and blood pressure seen in normal subjects [4], but in 26% of patients this was followed by a more prolonged period of hypotension and bradycardia, mimicking neurogenic syncope [5]. Therefore, intravenous adenosine has been suggested as a diagnostic test for neurogenic syncope, with a sensitivity equivalent to the tilt-isoproterenol test [6]. The specificity of this test, however, has not been adequately studied. The reported false-positive response rate in normal subject is 7%, but only 14 subjects were studied in the original report and these subjects were younger compared with patients [5].

Adenosine has also been proposed as a diagnostic tool to identify patients in whom spontaneous atrioventricular block contributes to syncope. A rapid intravenous bolus injection of 20 mg adenosine triphosphate (ATP) produced atrioventricular block or sinus arrest of greater than or equal to 10-s duration in 28–41% of patients with syncope of unknown origin [7,8]. This response was observed in only 5% of age-matched control subjects [8]. Atrioventricular block can be explained by the triggering of a vagal reflex induced directly by ATP [9], although some argue that it may be due to its conversion to adenosine [8]. It remains controversial whether a positive ATP test result identifies patients in whom event monitoring reveals spontaneous atrioventricular block as the actual cause of their syncope [8,10], but this test has been proposed as a way to identify patients with cardioinhibitory syncope who would benefit from pacemaker placement [11]. There is, however, no concordance between patients who test positive for tilt or ATP tests [12]. Furthermore, ATP-positive patients tend to be
older and have cardiac abnormalities. The so-called “adenosine or ATP-sensitive syncpe,” therefore, may reveal an underlying bradyarrhythmia which may or not be related to neurogenic syncpe.

These results raise the possibility that adenosine plays a role in the triggering of neurogenic syncpe, but this hypothesis had not been adequately tested. That was the main goal of the study published by Drs. Sinkovec, Grad, and Rokovec in this issue [13]. They reasoned that, if endogenous adenosine would contribute to neurogenic syncpe, then dipyridamole, by increasing endogenous adenosine levels, would increase the incidence of syncpe; conversely, theophylline would prevent tilt-induced neurogenic syncpe by blocking adenosine receptors. They used repeated tilt tests to explore the effects of these pharmacological probes. The limitations of tilt testing in the diagnosis of syncpe in general, and in determining effectiveness of treatment in particular, are beyond the scope of this editorial.

It is revealing, however, that about a half of their tilt-positive syncope patients had a subsequent negative tilt test result while on placebo. This and other results are summarized in Figure 1 of their article. Dipyridamole provoked neurogenic syncpe during head-up tilt in 57% of patients with a history of syncope and a previously negative tilt test result (their “moderately-sensitive subjects”), compared with 21% of patients with no history of syncope and a previously negative tilt test result (“non-sensitive subjects”). This phenomenon could be prevented with theophylline in 75% of cases, strongly suggesting that dipyridamole-induced syncpe was mediated by endogenous adenosine.

Dipyridamole, therefore, could be used in conjunction with head-up tilt to increase the “yield” of this test. It may be comparable to the tilt-isoproterenol test, which has approximately the same percentage of “additional-positive” and “false-positive” responses. Without a golden standard, however, it is difficult to determine if these “additional-positive” results truly identify patients who have neurogenic syncpe spontaneously. Furthermore, the authors concluded that endogenous adenosine was not involved in the triggering of tilt-induced syncpe, because theophylline was not effective in preventing syncope in patients with a history of syncope and a previously positive tilt test result (“sensitive subjects”). It should be noted, however, that both theophylline and placebo “normalized” the response to tilt in about 40% of subjects with a previous positive tilt test result.

The authors conclude that, even though dipyridamole can trigger syncpe during head-up tilt, endogenous adenosine probably does not play a role in neurogenic syncpe triggered by head-up tilt alone. This is a reasonable interpretation of their results, but alternative explanations should be considered. The authors acknowledge that theophylline has important actions in the central nervous system, and adenosine has multiple and often contradictory effects on autonomic cardiovascular regulation [14]. For example, blockade of central nervous system adenosine may lead to increase sympathetic activity, which may confound the interpretation of their results. It is also possible that endogenous adenosine is more important in patients with predominant cardioinhibitory syncpe, information not available in this report. Finally, theophylline is a relatively poor adenosine receptor antagonist with a narrow therapeutic window. It is a nonspecific antagonist at all four adenosine receptors, which probably explains its multiple side effects. The eventual availability of more potent and selective adenosine receptor antagonists, coupled with a better understanding of the underlying pathophysiology of the different forms of syncpe, may be required to adequately define the role of adenosine in this condition.

References