

## Adenosine and syncope: The conscious relationship?

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The first and single attack of presyncope or syncope can be endured with much effort, but recurrences strongly devastate health perception and turn a healthy person into an anxious and insecure patient.<sup>1</sup> Although in 50% of the patients presenting in the emergency department a diagnosis can be made after initial evaluation with history taking, physical examination, and electrocardiogram (ECG),<sup>2</sup> a battery of diagnostic tools is sometimes needed for identifying the cause of unexplained syncope. The final diagnosis varies among benign vasovagal collapse, neurocardiogenic syncope, cardiac arrhythmias, structural cardiopulmonary conditions, and neurologic, psychiatric, and metabolic disorders. The success rate of these examinations in terms of a certain or likely diagnosis is low depending on the methods, criteria, and experience of the investigators, creating a considerable cohort of patients with unexplained syncope.<sup>3</sup> If the diagnosis is certain or likely, the efficacy of current therapeutic measures such as medication<sup>4</sup> and leg crossing<sup>5</sup> for preventing or aborting new attacks of syncope is often disappointing. Thus more insight into the pathophysiology of the various types of syncope is strongly welcomed to provide tailored patient support.

In recent years, the intravenous bolus of adenosine triphosphate (ATP) has been evaluated as a rapid, easy, and cheap method to induce atrioventricular block and/or sinus arrest by creating a long RR interval and thus provoking syncope.<sup>6</sup> This approach might simulate the mechanism of unexplained syncope. Initially, the ATP test appeared to identify a specific group of syncope patients characterized by higher ages, fewer syncope attacks, lower incidence of situational, vasovagal, or triggering factors, and a higher prevalence of high blood pressure and ECG abnormalities than those with an isolated positive tilt test.<sup>7</sup> However, later studies pointed to the heterogeneity of the mechanisms of the positive ATP test and lack of predictive value for recurrent syncopal episodes.<sup>8,9</sup>

When neurally mediated syncope is considered, the results of tilt testing and ATP testing are not comparable.<sup>10</sup> In my experience, a reason for this difference is the application of the ATP test: the steepness of the slope showing the relationship between time of arrival and the ATP concen-

tration at the cardiac target site strongly determines the outcome of the test. A very rapid intravenous injection at a site not far from the target tissue, for example, the femoral vein, as is usually done during electrophysiological studies, determines the outcome. Despite the uncertainty about the value of the ATP test, *endogenous* adenosine has been documented to modulate syncope during tilt testing because adenosine plasma levels were higher in patients with a positive tilt test than in those with a negative one.<sup>11</sup> Furthermore, the adenosine plasma levels rose 50% compared with baseline during a positive tilt test. These data suggest that adenosine release can be a trigger for syncope provoked by tilt testing.

In this issue of *Heart Rhythm*, a new piece of information about the contribution of adenosine to syncope is presented by Carrega et al.<sup>12</sup> The results confirm higher adenosine plasma levels in patients with syncope provoked by tilt testing and a further significant rise during the test compared with patients with a negative tilt test. A new result from the Carrega et al study is the observation of the increased expression of adenosine 2A receptors and up-regulation in patients with syncope during tilt testing. However, the receptor affinity for adenosine and synthesis for mRNA did not differ between patients with or without syncope during tilt testing. The authors also claim that the increased levels of plasma adenosine reflect the cause rather than the consequence of the syncope during tilt testing and noticed that the increase of adenosine receptors is not associated with more adenosine synthesis.

To appreciate the message of this study, its limitations have to be taken into account. All results depend on a single tilt test. Although all included patients had more than one syncope episode, patient-to-patient variability can occur because of the low reproducibility of tilt testing<sup>13</sup> and might have affected the categorization of the responses to tilt testing. Second, the type of response to tilt testing such as an isolated cardiac-inhibitory, vasodepressive, or mixed one could not be related to adenosine plasma levels. This shortcoming should be attributed to the small sample size or the pretest-limited documentation of symptoms. The terminology applied in this study is somewhat confusing because the mechanism of vasovagally originated syncope can differ strongly from neurally mediated syncope. Therefore, it remains unclear whether patients without increased adenosine

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plasma levels and lower receptor expression did not have typical neurally mediated syncope or indeed suffer from a different mechanism of repetitive loss of consciousness. It is therefore too early to put the outcome of this study into diagnostic and/or therapeutic perspectives.

Because the authors could clearly rule out a mutation of the adenosine A2 receptor gene and showed that increased release of endogenous adenosine is the primary disorder in patients with syncope during tilt testing, whereas the increased expression of the receptors is of a secondary order, the mechanism of the increased synthesis awaits further study. Since the reflex syncopal syndromes are strongly related to changes of the autonomic tone, the amount and timing of adenosine release and its effects on the cardiac and vascular systems should be compared with more refined parameters of the autonomous status than tilt testing. This knowledge can clarify why diverse pharmacological approaches such as  $\alpha$ -adrenoreceptor agonists,  $\beta$ -adrenoreceptor antagonists, serotonin re-uptake inhibitors, and disopyramide show such inconsistent therapeutic benefit in clinical trials. In addition, the effectiveness of physical maneuvers for prevention or abortion of syncope can be tested with adenosine plasma levels in conjunction with changes of parameters of the autonomic nervous system.

Although a case report demonstrated the value of the adenosine antagonist theophylline in a patient with drug refractory syncope,<sup>14</sup> the xanthine derivatives can enhance adenosine synthesis and up-regulate the adenosine receptors and thus provoke loss of consciousness. One can safely assume that the patient with repetitive presyncope or syncope will not benefit from more cups of coffee. In the meantime, patient education, identification of syncope triggers, and reassurance remain the standard measures for the various types of reflex syncope with the awareness that tilt testing and the intravenous ATP bolus have limited diagnostic value and that implantable loop recorders can unmask arrhythmias as the mechanism of syncope. Whether adeno-

sine plasma levels will extend our diagnostic methods is currently pure speculation.

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