Adenosine test in the diagnosis of unexplained syncope: marker of conducting tissue disease or neurally mediated syncope?

Steve W. Parry1,2*, Samiran Nath3, John P. Bourke2,3, Rodney S. Bexton3, and Rose Anne Kenny1,2,4

1 Falls and Syncope Service, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne, NE1 4LP, UK; 2 School of Clinical Medicine, University of Newcastle Upon Tyne, Framlington Place, Newcastle upon Tyne, NE1 2DN, UK; 3 Department of Cardiology, Freeman Hospital, Freeman Road, Newcastle upon Tyne, NE7 7DN, UK; and 4 Trinity College, College Green, Dublin 2, Ireland

KEYWORDS
Syncope; Adenosine; Adenosine triphosphate; Sinus node; Atrioventricular block; Neurally mediated syncope

Received 7 September 2005; revised 27 January 2006; accepted 9 March 2006; online publish-ahead-of-print 30 March 2006

Adenosine is a ubiquitous purinergic nucleoside found in all living cells, with diverse physiological functions including heart rate, smooth muscle tone, glycolysis and lipolysis modulation, blood and endothelial cell regulation, and modulation of neurotransmission.1,2 When administered exogenously, adenosine has profoundly negatively chronotropic and dromotropic effects, actions which provide the basis for its use in the diagnosis and management of supraventricular tachyarrhythmias.1,3–5 More recently, adenosine [or the related precursor compound adenosine triphosphate (ATP)] has been highlighted in the European Society of Cardiology (ESC) guidelines for its diagnostic use in patients with unexplained syncope.6 The test has enormous advantages in terms of brevity and relative safety compared with electrophysiology (EP) studies but remains relatively poorly studied. The guidelines recommend a 20 mg bolus injection of adenosine during continuous haemodynamic and electrocardiographic (ECG) monitoring, with a positive test defined by the induction prolonged asystole (≥6 s) or high degree atrioventricular block (AVB) (≥10 s).6 However, given the paucity of clinical and experimental data on the use of adenosine in this context, the guidelines are cautious in their recommendations on the adenosine test, regarding it as ‘experimental’.6 Furthermore, there is no guidance on exactly what a positive adenosine test means, with various authors claiming that adenosine unmasks cardio-inhibitory vasovagal syncope (VVS) and others championing the test as a marker of sinus node disease or high degree AVB. In spite of this diagnostic confusion, several pacing intervention studies are underway in patients with syncope and a ‘positive’ adenosine test (Flammang, personal communication). In addition, controversy remains on the use of ATP vs. adenosine and on the duration of asystole and bradycardia required for a positive diagnosis to be made. These aspects of this ill-defined, controversial but highly promising test will be now examined in more detail. Throughout, the terms adenosine and ATP will be used interchangeably depending on the drug used in the study under discussion.

Sources and selection criteria
In this article, we highlight the use of adenosine/ATP in the diagnosis of unexplained syncope. We searched Pubmed/ Medline and Cochrane databases using the keywords ‘adenosine’, ‘ATP’, ‘syncope’, ‘vasovagal’, ‘vasodepressor’, ‘sinus node’, ‘AVB’, ‘carotid sinus’, ‘neurally mediated’, ‘diagnosis’, and ‘test’. We also derived information from product literature.

Adenosine test and VVS
The role of adenosine in the vasovagal response has been explored in both animal and human studies. Waxman and Asta7 developed a rat model for VVS, with occlusion of the inferior vena cava (IVC) resulting in hypotension and a tachycardia which becomes a paradoxical bradycardia...
during concomitant isoproterenol infusion. Dipyridamole (an inhibitor of adenosine uptake which potentiates its action) administration allowed paradox bradycardia to occur at a much lower dose of isoproterenol and enhanced the bradycardic response to IVC occlusion, whereas aminophylline (an adenosine receptor antagonist) inhibited paradoxical bradycardia. They speculate that adenosine may augment sympathoinhibition in the effluent limb of the vasovagal response, providing an experimental framework for the use of adenosine in the diagnosis of VVS.\textsuperscript{7} One human study offers support for this notion, with higher plasma adenosine levels during positive head-up tilt testing in patients with VVS alongside a positive correlation between rising plasma adenosine concentration and rapidity of symptom onset.\textsuperscript{3}

Several studies have directly addressed the use of adenosine as a provocative agent during head-up tilt table testing (HUT) in the diagnosis of VVS. Shen \textit{et al.}\textsuperscript{9} administered 6 mg of adenosine (followed by 12 mg if there was no vasovagal response) immediately after 15 min 65° passive tilt in 85 subjects who also underwent isoproterenol provocation and compared them with 14 much younger healthy controls (61 vs. 38 years). The adenosine tilt test sensitivity was 67% compared to 88% with isoproterenol, whereas the 12 mg dose was more likely to induce VVS than 6 mg.\textsuperscript{9} Only one control subject suffered VVS with adenosine. Similar results were reported by Perez-Paredes \textit{et al.}\textsuperscript{10} using successive doses of 3, 6, and 9 mg of ATP.

In the late 1990s, Flammang \textit{et al.}\textsuperscript{11-14} published several landmark studies on the 20 mg ATP test in the diagnosis of VVS. Their original report on the results of supine ATP testing in 316 patients with unexplained syncope and 51 (again much younger) control subjects.\textsuperscript{11} Only three control subjects experienced a cardiac pause in excess of 10 s, whereas 74% (234) of syncopal patients had pauses of varying degrees with ATP, 84% of whom had third degree AVB and 16% sinoatrial (SA) block. One hundred and thirty (41%) were regarded as having an abnormal test (i.e. >10 s cardiac pause).\textsuperscript{11} The underlying mechanism was attributed to VVS with a profound cardiac component, though none of the patients underwent tilt table testing to help confirm or refute the diagnosis. There was similarly no discussion based on the possibility of the test unmasking conducting tissue disease.\textsuperscript{11} Flammang \textit{et al.}\textsuperscript{11} also noted a significant increase in ATP test positivity rates with increasing age, but fail to mention this in the context of their much younger control group. One year later, Flammang \textit{et al.}\textsuperscript{12} published uncontrolled ATP test reproducibility data in 80 subjects with unexplained syncope, demonstrating reproducible prolonged pauses in 88% of subjects at 7 days and 78% of subjects at a mean of 3.7 years. The same group then published uncontrolled, non-randomized data on 72 patients with unexplained syncope undergoing passive tilt testing (followed by isoproterenol provocation if negative) and then ATP testing.\textsuperscript{13} Forty-one (57%) had a positive HUT, eight (11%) a positive ATP test, but only three were positive on both tests.\textsuperscript{13} Despite such marked diagnostic discordance, the authors maintained that the ATP test was a marker for cardio-inhibitory VVS.\textsuperscript{13} The most recent contribution of Flammang \textit{et al.}\textsuperscript{14} was a randomized pacing intervention study in 20 older subjects with unexplained syncope, with event-free survival of an impressive 52 months in the paced group. A larger multi-centre study is currently underway and is awaited with interest (Flammang, personal communication).

Mittal \textit{et al.}\textsuperscript{15} compared three different adenosine tilt protocols with standard testing in 201 patients with unexplained syncope/pre-syncope, with adenosine positivity defined by the induction of a characteristic vasovagal response. Adenosine tilt provided a similar diagnostic yield to conventional testing, but again there was a marked discordance between the two tests; of the 31 patients with a positive tilt test, nine were positive only with adenosine and 12 during routine tilting.\textsuperscript{15} The authors suggest that this finding provides evidence of complimentary roles for the two tests.\textsuperscript{15} They later examined a single-stage adenosine tilt test in patients with unexplained syncope.\textsuperscript{16} A 3 min adenosine tilt test in 129 patients and 30 control subjects yielded an overall specificity of 100%, but very low diagnostic yield (18%). Despite speaking of ‘specificity’, there was no conventional tilt test to compare adenosine tilt testing with,\textsuperscript{16} although positivity was arbitrarily defined as a vasovagal event following the reflex tachycardia seen post-adenosine administration. On post hoc analysis, the authors found that the greatest yield was in those under 40 years of age,\textsuperscript{16} but in the absence of a pre-planned controlled study, these findings must be open to question.

Brignole \textit{et al.}\textsuperscript{17,18} examined the role of supine ATP administration in the diagnosis of ‘neurally mediated syncope’ and sinus node disease and later tilt-positive VVS. In their original study, 20 mg of ATP was infused into 79 patients (mean age 71 years) with neurally mediated [tilt-positive VVS or carotid sinus syndrome (CSS)] syncope, sinus node disease or both, and 31 controls (mean age 62 years).\textsuperscript{17} ATP test positivity was the same in all groups, with similar degrees of AVB in both patients and controls.\textsuperscript{17} The group more recently reported on 175 patients with unexplained syncope who underwent ATP and HUT.\textsuperscript{18} Of the 121 patients with a positive test, 77 (64%) were head-up tilt positive, 18 (15%) ATP positive (defined by a ventricular pause >6 s or AVB >10 s) and 26 (21%) both. ATP-positive patients were older, had more cardiovascular co-morbidity, less frequent syncope episodes, and fewer vasovagal-type triggering factors, whereas AVB accounted for 43 of the 44 positive tests.\textsuperscript{18} The authors concluded that adenosine-sensitive syncope was a different entity to VVS and that the ATP test could not be used as a substitute for HUT.\textsuperscript{18}

**Adenosine test and sick sinus syndrome**

Brignole \textit{et al.}\textsuperscript{17} first examined the potential role of ATP in the diagnosis of sinus node disease as described earlier. Although they felt that intrinsic sinus node disease was a necessary pre-condition for adenosine-induced sinus arrest in either neurally mediated syncope or sick sinus syndrome (SSS), the adenosine test was not able to diagnose SSS per se.\textsuperscript{17} In a later small study, Burnett \textit{et al.}\textsuperscript{19} administered 0.15 mg/kg adenosine to 10 patients with SSS (diagnosed non-invasively in nine, via EP studies in one) and 67 age-matched controls undergoing EP for other reasons. Sensitivity for the diagnosis of SSS with adenosine was 80% and specificity 97%,\textsuperscript{19} comparing well with, for example, tilt table testing.\textsuperscript{20} An accompanying editorial reviewed the test favourably, but with the proviso that further work need to be done before its widespread adoption.\textsuperscript{21}
Adenosine test and high-degree AVB

Although their original study showed similar degrees of AVB following ATP administration in subjects with neurally mediated syncope and SSS, Brignole et al. later published data suggesting that the ATP test could be used to diagnose AVB as the cause of symptoms in patients with unexplained syncope. They administered a 20 mg bolus of ATP to 60 patients (57 ± 19 years) with unexplained syncope and 90 asymptomatic, age-matched controls. The upper 95th percentile for the maximal R–R interval in the control group was 6000 ms in the control group, forming the basis for the ESC’s tentative guidance. In the second part of their study, asystole was recorded during spontaneous syncope in 24 of the patient group and was due to sinus arrest in nine and AVB in 15. ATP injection induced asystole > 6 s in 53% of the AVB group but in none of those with sinus arrest. On the basis of these results, the group suggested that patients with unexplained syncope have a higher susceptibility to ATP testing and that the ATP test may identify those with paroxysmal AVB. The same group’s most recent data throw these results into doubt. Donato et al. placed implantable loop recorders into 36 ATP-positive patients (69 ± 10 years), 15 of whom had positive tilt table tests. Eighteen had symptom recurrence, and although most had bradycardia documented, the underlying mechanisms were manifold. ATP positivity predicted AVB in only a few patients.

Adenosine test and CSS

Exogenous adenosine has long been known to excite carotid chemoreceptors in animal models. Adenosine is thought to facilitate the baroreflex, with the main physiological effects including a decrease in heart rate and blood pressure which was abolished by inactivation of the carotid body or section of the carotid sinus nerve. These physiological effects have not been studied in humans, and although Brignole et al. studied several patients with CSS, their study design precluded an examination of the role of adenosine/ATP in the diagnosis of CSS. The induction of > 3 s asystole during carotid sinus massage is essential for the diagnosis of the cardio-inhibitory forms of CSS, and it may be that the prolonged asystole induced by a positive adenosine test is a marker for CSS.

Adenosine or ATP?

Although the ESC guidelines adopt an either/or approach to the use of adenosine or ATP in this context, several authors have suggested that only ATP can cause the initial vagal afferent excitation necessary to reliably elicit a response. This notion is based on the work of one laboratory over the last 20 years, with an eloquent series of experiments in dogs clearly showing that ATP exerts vagal effects independent of its rapid degradation to adenosine, though with the caution that the biologically active breakdown products of ATP all contribute to its action. Others had already shown that such vagal enhancement was dependent on the route of administration, with intra-coronary injection of ATP producing none of the effects noted by Pelleg, during intra-right atrial administration. Similarly, there is no bradycardia when non-hydrolysable ATP is injected directly into the sinus node artery, implying that conversion to adenosine is necessary for its action. The vagal role of ATP may also be species-specific. Although it has clear actions in canine models and cat models, degradation of ATP to adenosine is necessary for its actions on the guinea pig AV node. Generalizability to humans must thus remain open to speculation. Where adenosine and ATP have been compared in the therapeutic rather than diagnostic arena, there is little to choose between the two agents. In a review of seven studies, Belhassen et al. found equal efficacy and tolerability for ATP and adenosine in the management of supraventricular tachyarrhythmias. There is thus no convincing evidence that ATP is preferable to adenosine in human subjects.

Safety, tolerability, and drug interactions of adenosine

Adenosine’s main side effects are attributable to its negatively chronotropic and dromotropic effects with light-headedness, pre-syncope and syncope reported, as well as flushing, breathlessness, chest pressure, and nausea. Less commonly sweating, blurred vision, headache, and generalized ‘discomfort’ are noted. The symptoms are generally short lived because of the rapid degradation of adenosine to metabolically inactive compounds. Bronchospasm may be induced in those with asthma or chronic obstructive pulmonary disease. The pro-arrhythmic effects of adenosine over the 13 years since its introduction in the United States in 1989 were comprehensively reviewed by Pelleg et al. in a recent paper. While commenting on the ‘excellent safety record of adenosine and ATP’ in the published literature, Pelleg et al. found supraventricular tachyarrhythmias (largely atrial flutter/fibrillation) following adenosine administration in 12 patients (six of whom had accessory pathways), torsade de pointes in six (all of whom had long QT intervals), and ventricular fibrillation in one patient. Unpublished data from the manufacturer showed a further 21 cases of ventricular tachyarrhythmias in patients ranging from 29 to 86 years of age. In the studies reviewed above, of the 1293 patients and 296 controls, the only complications were atrial fibrillation in eight patients and three control subjects (duration unspecified) and non-sustained atrial tachycardia in one patient. The actions of adenosine are enhanced by dipyrade, which antagonizes the effect of adenosine on the myocardium.

Conclusion

The underlying diagnosis indicated by a positive adenosine test therefore remains elusive. Each of the potential diagnoses above has some evidence to support it (Table 1), but...
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Definition of positive test</th>
<th>No. of patients (mean age)</th>
<th>No. of controls (mean age)</th>
<th>Positivity/sensitivity/specificity (controls)</th>
<th>No. of controls positive</th>
<th>Drug</th>
<th>Dose (mg)</th>
<th>Mean duration asystole (s) patients/controls</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brignole et al.</td>
<td>VVS, SSS</td>
<td>NR</td>
<td>79 (71 years)</td>
<td>31 (62 ± 16 years)</td>
<td>ATP non-diagnostic</td>
<td>0 (transient AVB 45%)</td>
<td>ATP</td>
<td>20</td>
<td>3.6/(none)</td>
</tr>
<tr>
<td>Shen et al.</td>
<td>VVS</td>
<td>'VVS'</td>
<td>85 (61 years)</td>
<td>14 (38 years)</td>
<td>67% sens adenosine 88% sens isoproterenol</td>
<td>1 (7%)</td>
<td>Adeno</td>
<td>6/12</td>
<td>'VVS'</td>
</tr>
<tr>
<td>Flammang et al.</td>
<td>CIVVS</td>
<td>10 s asystole</td>
<td>316 (74 years)</td>
<td>51 (56 years)</td>
<td>130 (41%) [3 (6%) ctrl]</td>
<td>3 (6%)</td>
<td>ATP</td>
<td>20</td>
<td>20.5 ± 0.7/ (13.3 ± 0.7)</td>
</tr>
<tr>
<td>Brignole et al.</td>
<td>6 s asystole</td>
<td>60 (57 years)</td>
<td>90 (55 years)</td>
<td>Not stated</td>
<td>ATP</td>
<td>20</td>
<td>NR for whole group</td>
<td>One non-sustained atrial tachy</td>
<td></td>
</tr>
<tr>
<td>Flammang et al.</td>
<td>CIVVS</td>
<td>10 s asystole</td>
<td>80 (72 years)</td>
<td>None</td>
<td>NA</td>
<td>No ctrl</td>
<td>ATP</td>
<td>20</td>
<td>None</td>
</tr>
<tr>
<td>Perez-Paredes et al.</td>
<td>VVS</td>
<td>'VVS'</td>
<td>30 (37 years)</td>
<td>13 (35.5 years)</td>
<td>9 (30%) iso + 7 (23%) ATP + 2 (7%) both, [1(3%) both]</td>
<td>1(8%)</td>
<td>ATP</td>
<td>3/6/9</td>
<td>'VVS'</td>
</tr>
<tr>
<td>Flammang et al.</td>
<td>CIVVS</td>
<td>10 s asystole</td>
<td>72 (65 y)</td>
<td>None</td>
<td>41 (57%) HUT + 8 (11%) ATP +, 3 both Pacing study Adeno and iso comparable</td>
<td>No ctrl</td>
<td>ATP</td>
<td>20</td>
<td>17.2 ± 1.8</td>
</tr>
<tr>
<td>Flammang et al.</td>
<td>CIVVS</td>
<td>10 s asystole</td>
<td>20 (72 years)</td>
<td>201 (55 years)</td>
<td>None</td>
<td>Adeno vs. tilt ± iso</td>
<td>No ctrl</td>
<td>ATP</td>
<td>20</td>
</tr>
<tr>
<td>Mittal et al.</td>
<td>VVS</td>
<td>'VVS'</td>
<td>10 s asystole</td>
<td>None</td>
<td>80% sens 97% spec</td>
<td>2 (3%)</td>
<td>Adeno</td>
<td>0.15 mg/kg</td>
<td>Max 11.8 s with adeno</td>
</tr>
<tr>
<td>Burntett et al.</td>
<td>SSS</td>
<td>SSS CSNRT t &gt; 550 ms</td>
<td>10 (71 years)</td>
<td>67 (59 years)</td>
<td>77 (64%) HUT + 18 (15%) ATP + 26 (21%) both</td>
<td>No ctrl</td>
<td>ATP</td>
<td>20</td>
<td>NR</td>
</tr>
<tr>
<td>Brignole et al.</td>
<td>VVS, ASS</td>
<td>6 s asystole</td>
<td>175 (121 +) (HUT 45 years) (ATP 68 years) (Both 58 years)</td>
<td>None</td>
<td>Multiple underlying diagnoses</td>
<td>No ctrl</td>
<td>ATP</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Donateo et al.</td>
<td>ILR post-ATP</td>
<td>6 s asystole</td>
<td>36 (69 years)</td>
<td>None</td>
<td>18% +, 100% spec</td>
<td>0</td>
<td>Adeno</td>
<td>150 μg/kg</td>
<td>'VVS'</td>
</tr>
<tr>
<td>Mittal et al.</td>
<td>VVS</td>
<td>'VVS'</td>
<td>129 (54 years)</td>
<td>30 (30 years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Studies are cited in chronological order. Controlled studies in bold. sens, sensitivity; spec, specificity; AF, atrial fibrillation; NA, not applicable; +, positive; adeno, adenosine; iso, isoproterenol; 'VVS', vasovagal response; CI, cardioinhibitory; pts, patients; ctrl, controls; NR, not recorded; NFU, no follow-up/record of duration of complication; ASS, adenosine-sensitive syncope; ILR, implantable loop recorder; CSNRT, corrected sinus node recovery time.
none has the weight of a definitive study to promote its widespread use. The pathophysiological effects of adenosine offer little further help, exogenous adenosine has well-documented effects on the sinus node, although its most powerful negatively chronotropic and dromotropic effects are exerted on AV conduction. The rationale for adenosine’s role in VVS has merit in terms of mimicry of the sympathetic excitation commonly seen prior to VVS, but its part in the initiation of the response is far from clear. The studies described have variable methodologies, no power calculations to back up their study numbers and small, often significantly younger control groups in the studies in which they are present (totaling only 296 in all studies reported to date). The design of several of the papers involves sub-studies with even smaller numbers of subjects. Moreover, confusion remains regarding the use of adenosine vs. ATP, the dosage used (arbitrarily defined as 20 mg), and the ECG criteria needed for a positive test. Clearly, much further work is needed before the adenosine test is widely adopted as a diagnostic test in the unexplained syncope workup, with particular emphasis on the underlying pathophysiology exposed by a putatively positive adenosine test. Although ‘adenosine-sensitive syncope’ remediable with permanent pacing remains a possibility, the test cannot be routinely recommended until such work is published.

Conflict of interest: none declared.

References