The intravenous adenosine test: a new test for the identification of bradycardia pacing indications? A pilot study in subjects with bradycardia pacing indications, vasovagal syncope and controls

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Summary

Background: Intravenous adenosine has recently been used in the diagnosis of unexplained syncope, but there is no consensus as to the meaning of a ‘positive’ test. The objective is to determine the sensitivity and specificity of intravenous adenosine testing in the diagnosis of bradycardia-pacing indications [sinus node dysfunction (SND), atrioventricular block (AVB) and cardio-inhibitory carotid sinus syndrome (CSS)].

Design: Pilot cohort study.

Methods: Patients—(i) Bradycardia-pacing group: Consecutive patients referred for pacing for SND, AVB and CSS; (ii) Consecutive head-up tilt (HUT)-positive VVS patients. Controls—(i) Simple controls (S-Con: normal examination/ECG) and (ii) Electrophysiology controls (EP-Con: consecutive subjects referred for accessory pathway ablation). Pacing referrals and EP-Con had electrophysiology studies to confirm referral diagnosis and exclude others. All subjects had bolus injection of 20 mg intravenous adenosine during continuous ECG and blood pressure monitoring (positive test: ≥6 s asystole, ≥10 s high-degree AVB post-injection). Sensitivity, specificity, safety and tolerability of the test were measured.

Results: Of 264 potential participants (4 SND, 8 AVB, 7 CSS, 10 VVS, 10 EP-Con and 11 S-Con) 50 were studied. All (100%) of the bradycardia-pacing group were adenosine test-positive, as were 6 (60%) VVS. None (0%) and 3 (27%) of the EP- and S-Con groups were positive. Adenosine testing was 100% sensitive and 86% specific for bradycardia-pacing indications, and 100% specific using the diagnostically ‘clean’ EP-Con results. There were no significant adverse or side effects.

Conclusions: Adenosine testing reliably identified patients with definitive bradycardia-pacing indications in whom alternative diagnoses were excluded. Further work is needed to evaluate the role of this test in the diagnosis of unexplained syncope.
Introduction

Intravenous adenosine and its precursor adenosine triphosphate (ATP) have recently been proposed as diagnostic tools in the evaluation of unexplained syncope.1–16 The test (supine administration of a 20 mg intravenous bolus with electrocardiographic and blood pressure monitoring) is simple, quick, cheap and safe and has the potential to revolutionise diagnostic pathways in syncope, but there is no consensus as to the underlying diagnosis exposed. Vasovagal syncope (VVS),1–11 sinus node dysfunction (SND),10,12,13 atrioventricular block (AVB)14,15 and cardio-inhibitory carotid sinus syndrome (CSS)16 have all been proposed as putative diagnoses exposed by a positive adenosine test (i.e. >6 s ventricular asystole or >10 s high degree AV block following administration of the drug17). Several authors favour cardio-inhibitory VVS as the likely underlying diagnosis,4–7 though more recent work observing the relationship between head-up tilt results with real time ECG recording during spontaneous syncope shows no correlation between ATP test results and the mechanism (cardio-inhibition versus vasodepression) of neurally mediated syncope.18 Accordingly the European Society for Cardiology (ESC) advises no treatment on the basis of adenosine or ATP testing ‘until a definite mechanism of syncope can be obtained’,17 while there is no pacing indication for positive adenosine testing in the American College of Cardiology/ American Heart Association19 or ESC20 pacing guidelines.

The older age of the patients in the largest series studied to date (mean 74 years),4–7 the physiological sites of action of the drug (atrioventricular node, and less actively the sinus node)21 and preliminary data showing benefit in pacing intervention studies7 led us to the original hypothesis that a positive adenosine test identifies generic bradycardia pacing indications, though others have spoken of a less specific ‘adenosine sensitive syncope’11 or specifically associated a positive test with SND10,12,22 or AVB.14 There have been no previous attempts to examine the rationale for adenosine testing in patients with these conditions in whom alternative diagnoses have been definitively excluded. Our aims were therefore first, to see whether a positive adenosine test identified patients with such pacing indications correctly (SND, high degree AVB and CSS) and/or those with VVS, in patients with definitive diagnoses of these conditions and control subjects; and secondly to assess the safety and tolerability of the procedure.

Methods

Participants were divided into Subject groups and Control groups and recruited from September 2004 to October 2005.

Subject groups

Subjects were recruited into two diagnostic study groups:

(1) Bradycardia pacing indications: SND, atrio-ventricular block (AVB), cardioinhibitory carotid sinus syndrome:
Consecutive patients referred for pacemaker implantation for these bradycardia pacing indications to our pacing service were prospectively identified. Diagnoses were made on the basis of conventional testing including surface ECG, 24-h ambulatory monitoring, external and internal loop recording, electrophysiology studies (EPS) and carotid sinus massage (CSM).

(2) Vasovagal syncope: Consecutive patients were identified following the exclusion of alternative causes of syncope and a positive head-up tilt table test (HUT) at our tertiary referral syncope facility.

Control groups

Two control groups were studied:

(1) ‘Simple’ Controls (S-Con)
Control subjects volunteered in response to an advertisement placed in various locations in the study hospitals and the University.

(2) Electrophysiology controls (EP-Con)
Consecutive patients referred for accessory pathway catheter ablation by electrophysiological study (EPS) to the electrophysiology service were identified, with inclusion subject to a successful procedure and absence of conducting tissue disease.

Inclusions

Subjects and controls were over the age of 18 years. Each eligible participant was contacted by telephone to give initial information about the study and to gain consent to send more detailed information. Willing participants were then formally enrolled into the study with evaluation of history, physical examination, ECG and written consent obtained.

Exclusions

Participants were excluded if they had persistent or permanent atrial fibrillation, asthma or chronic
obstructive pulmonary disease (COPD), severe coronary disease (known coronary stenosis >70%, New York Heart Association (NYHA) heart failure or angina symptoms Class III or IV), known severe cerebrovascular disease, myocardial infarction within 3 months, prolonged corrected QT interval, unablated accessory pathway, pregnancy or lactation, use of dipyridamole or any rate-limiting medication, hypertrophic cardiomyopathy, cardiac transplantation or known significant internal carotid artery stenosis (>50%), or if they were unable to give informed consent. S-Con were excluded if they had surface ECG abnormalities or evidence of structural heart disease.

**Diagnostic pathway prior to adenosine testing**

This is summarized in Figure 1. The purpose of this pathway was to: (i) Enrol participants with the above diagnoses to the study and (ii) ensure diagnostic purity, i.e. that they had only the diagnosis attributed to them and no other. Accordingly, each participant entered the study in one of the six ‘diagnostic’ columns. Prior to receiving adenosine, all subjects in the diagnostic groups underwent testing to ensure that their original diagnosis was robust and to the exclusion of all others, with the exception of VVS and S-Con, who did not undergo EPS. If patients straddled two or more diagnostic categories they were excluded from the study. If testing showed the participant to be exclusively in another diagnostic category, this was reflected in their final diagnostic grouping at the time of receiving adenosine. EP-Con were excluded if they had any evidence at EPS of conducting tissue disease or subsequently of CSS or VVS during CSM and tilt studies.

**CSM**

Subjects in the SND, AVB and VVS groups, and controls in the EP-Con group, who were above the age of 40 years, were considered for bilateral, sequential, supine then erect CSM during beat-to-beat blood pressure and ECG monitoring (TaskForce Monitor, CN Systems, Austria). CSS patients had already undergone CSM as part of their diagnostic work-up.

**Head up tilt table testing**

Subjects in the SND, AVB and CSS groups, and controls in the EP group underwent conventional HUT. VVS patients had already undergone testing to make the diagnosis.

**Limited electrophysiology study**

All bradycardia pacing indication subjects and the EP-Con group underwent limited EPS at the time of their procedure. This was done using the EP catheters for the EP-Con group, or the newly implanted pacemaker leads in the pacemaker patients. The following parameters were tested to assess sino-atrial (SA) node and AV node function respectively:

- Corrected sinus node recovery time (CSNRT): after a trial pacing at one long cycle length, and two shorter cycle lengths, the time to recovery of the sinus node was measured. An abnormal CSNRT was defined as >550 ms, suggesting SA node dysfunction.
- Wenkebach point: atrial pacing at progressively shorter cycle lengths produces progressive slowing of AV node conduction, until a point is reached where the Wenkebach phenomenon is observed. Where a prematurely long cycle length induces Wenkebach, this suggests AV node dysfunction. An abnormal Wenkebach point was defined as a cycle length >460 ms. More detailed study of AV node and His-Purkinje function was of course not possible given
the method of performing these studies at the time of permanent pacing.

Adenosine testing

Procedure
Following counselling regarding expected symptoms during testing, a 20 mg bolus of adenosine (Adenocor, Sanofi-Synthelabo) was administered via an antecubital vein (followed by a 20 ml flush of 0.9% saline) with continuous ECG and blood pressure monitoring.

Safety
Advanced cardiac life support equipment, high flow oxygen and salbutamol nebulisers were immediately available in all cases. For the bradycardia pacing and EP-Con groups a back-up external pacemaker (ventricular pacing) was connected via the newly implanted leads (or the EPS catheters for the EP-Con group) if subjects experienced asystole of \( \geq 20 \) s. External non invasive pacing was available for the VVS and S-Con groups.

Adenosine test positivity
A positive test was defined per ESC guidelines, namely ventricular asystole \( \geq 6 \) s, and/or 2nd/3rd degree AV block \( \geq 10 \) s following injection. An intra-cardiac electrogram was also recorded for subjects with pacemakers and the EP-Con group.

Symptoms and any requirement for temporary pacing were also recorded.

Statistical analysis and sample size
Positivity rates and sensitivity and specificity of adenosine testing for bradycardia pacing indications were calculated. We aimed to recruit 15 patients to each patient and control group; this was a pragmatic decision based on what was a realistic number to collect. As the study is exploratory in nature it was not powered to detect specific differences in specificity and sensitivity.

The study was approved by the Local Research Ethics Committee.

Results
Fifty (19%) of 264 eligible participants underwent adenosine testing. The recruitment process showing inclusions and reasons for exclusion is summarized in Figure 2. Subjects in the ‘other’ category [29 (11%)] were excluded on the basis of significant ischaemic heart disease, inability to give consent, previous cerebrovascular disease or ineligibility due to being too young. In the bradycardia pacing indication group, one patient in each of the SND, AVB, CSS groups were excluded at the time of the procedure. The AVB patient had no evidence of AV node disease on testing; the SND and CSS patients each were found to have mixed diagnoses.

Age and sex of participants and the results of adenosine administration are shown in Table 1. Adenosine testing was 100% sensitive and 86% specific for bradycardia pacing indications. Using EP-Con results without S-Con, specificity was 100%. In addition, there was no relationship between degree of cardio-inhibition during head-up tilt testing and adenosine test positivity in the VVS group; the only patient with asystole during tilt testing [Vasovagal Syncope International Study (VASIS) classification \(^{17} \) IIa] had a negative adenosine test, and while two patients with mixed responses (VASIS I) had a positive adenosine test, four of the six patients with a pure vasodepressor response during tilt (VASIS III) were adenosine positive.

Adenosine testing took no more than 15 min from start to finish, with a cost per vial of approximately £2.00 ($4.00). There were no serious complications of adenosine administration. Symptoms described were predominantly of chest tightness, a warm flush and shortness of breath. These lasted no longer than 2 min and were not specific to any particular diagnostic group. Four subjects had pre-syncope but there was no syncope. Of the patients in the pacemaker groups 7 required temporary pacing until sinus rhythm was restored, and none in the EP-Con group. No VVS or S-Con participants required external pacing. One subject developed transient atrial fibrillation and this spontaneously reverted to sinus rhythm within 60 s, without the need for further intervention.

Discussion
Intravenous adenosine testing was highly sensitive and specific for bradycardia pacing indications in this small but tightly defined cohort, with 100% sensitivity and 86% specificity for bradycardia pacing indications; using only the diagnostically ‘pure’ EP-Con control group (i.e. those with conducting tissue disease and neurally mediated disorders definitively excluded) specificity rose to 100%. This is the first time such a study has been attempted, and the first to provide a rationale for both the test and future randomized studies of pacing intervention in those with a positive adenosine test. The rigour with which we excluded alternative diagnoses is a particular strength of our study; the conflicting conclusions on the underlying diagnoses exposed by a
Figure 2. Recruitment. A Fib: atrial fibrillation.

Table 1  Characteristics of ‘diagnostic’ test groups with positivity, sensitivity and specificity of adenosine testing

<table>
<thead>
<tr>
<th>Diagnostic group</th>
<th>Numbers receiving adenosine (n)</th>
<th>Mean age (SD)</th>
<th>Females (%)</th>
<th>Positive test (n,%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SND</td>
<td>4</td>
<td>76 (5.8)</td>
<td>(75)</td>
<td>4 (100)</td>
<td>100</td>
<td>na</td>
</tr>
<tr>
<td>AVB</td>
<td>8</td>
<td>71 (14.6)</td>
<td>(25)</td>
<td>8 (100)</td>
<td>100</td>
<td>na</td>
</tr>
<tr>
<td>CSS</td>
<td>7</td>
<td>77 (5.5)</td>
<td>(57)</td>
<td>7 (100)</td>
<td>100</td>
<td>na</td>
</tr>
<tr>
<td>VVS</td>
<td>10</td>
<td>57 (19.0)</td>
<td>(80)</td>
<td>6 (60)</td>
<td>60</td>
<td>na</td>
</tr>
<tr>
<td>EP-Con</td>
<td>10</td>
<td>38 (14.6)</td>
<td>(80)</td>
<td>0 (0)</td>
<td>na</td>
<td>100</td>
</tr>
<tr>
<td>S-Con</td>
<td>11</td>
<td>36 (12.9)</td>
<td>(36)</td>
<td>3 (27)</td>
<td>na</td>
<td>73</td>
</tr>
</tbody>
</table>

*Per European Society of Cardiology diagnostic criteria—see text; sensitivity for bradycardia pacing indication and VVS groups.

Inc: including; Exc: excluding; NA: not applicable.
Suggested by Brignole and colleagues in 2000, the suggestion of an ‘adenosine sensitive syncope’ abounds in the literature surrounding this test, with unexplained syncope. Canine and feline models support the notion that the initial vagal action of ATP prior to its hydrolysis to adenosine is essential in the use of the compound in syncope diagnosis, though this is clearly not the case in the guinea pig. There are no clear data to support the necessity of this initial vagal action in human studies; indeed the equal efficacy of ATP and adenosine in the management of supraventricular tachycardia (SVT) suggests the contrary. ESC guidance similarly agrees that ATP and adenosine are equivalent in their actions in this context. Our results show clearly that adenosine testing using the ESC definition of positivity provides a powerful method of identifying bradycardia pacing disorders without the need for ATP (though we did not attempt a head-to-head comparison).

Safety and tolerability

Adenosine testing was quick and easy to administer, cheap, well-tolerated despite its expected side effects and had no serious adverse effects, in keeping with previous literature on the test and its safety record in SVT management. There have been no significant adverse events recorded in more than 1500 patients reported to have undergone adenosine testing to date despite its use in frequently elderly patients. Nonetheless, prolonged hypotension can theoretically precipitate steal phenomena in patients with critical cerebrovascular or coronary disease, and as per ESC guidance, it is prudent to avoid adenosine testing in such individuals. We arbitrarily defined 20 s asystole as the cut off point for temporary pacing in patients who already had their permanent pacing wires in place, and using this criterion seven were paced for a few seconds. It is commonplace to see asystole of up to 60 s during tilt table testing without the need for intervention. None of the vasovagal or control subjects required pacing, in keeping with previous studies, suggesting that temporary pacing is unnecessary in this group, with the proviso that external pacing be available as an added precaution.

Study limitations

The main limitation of our study was the poor recruitment rate, with only 50 (19%) of the 264 individuals identified as potential participants eventually enrolling. The study’s greatest strength, the diagnostic purity of the diagnostic groups and EPCon, was also its Achilles’ heel, with 38 (14%) excluded because of atrial fibrillation and a total of 31 (12%) excluded because of competing diagnoses, structural heart disease and further investigations precluding participation (Figure 2). There were also a large number of exclusions because of...
contraindications to adenosine and consent issues [24 (9%) with asthma/COPD and 29 (11%) others as detailed above]. If the test were to become part of routine clinical practice many of these factors would become relative rather than absolute contraindications, with a more balanced approach depending on individual patient risks and benefits.

There was also a high level of refusal to participate on the part of eligible individuals [86 (33%)], partly because of the risks and side effects of adenosine but more commonly because of the risks associated with CSM. Our routine practice is to consent for this procedure on the basis of a 1:1000 risk of stroke,[30] a small risk that participants in an experimental study with no personal benefit were unwilling to take.

Further limitations included a difficult to explain female preponderance within most of the study and control groups as well as the younger age of the EP and simple control groups. Any further studies must include older control subjects to avoid confounding from this source. Statistical analysis of these parameters was not performed because of the small numbers and the potential to mislead with inappropriate testing. Bradycardia pacing indications tend to be problems for the elderly, while EP ablation for accessory pathways tends to be used in younger patients.

Conclusion

In this small preliminary study, we have shown that adenosine testing is highly sensitive and specific in identifying underlying bradycardia pacing indications. The test may have potential in the early diagnosis of these conditions, either in isolation or as part of a risk stratification strategy to fast-track those with a positive test to further investigations targeting bradyarrhythmias. Our methodological rigour and final results provide a more rational platform than previously available to help guide future studies based on adenosine testing.

References


