Use of Adenosine Test for the Exclusion of Preexcitation Syndrome in Asymptomatic Individuals

Alon Grossman, M.D.,* Ori Wand, M.D.,* Shlomi Matezki, M.D.,†
Arthur Kerner, M.D.,‡ Amit Assa, M.D.,* and Michael Glikson, M.D.†

From the *Israeli Air Force Aeromedical Center, Tel Hashomer, Israel; †Leviev Heart Center, Sheba Medical Center and Tel Aviv University, Tel Hashomer, Israel; and ‡Rambam Cardiology Center, Haifa, Israel

Background: Resting electrocardiogram is a routine procedure for the identification of potentially fatal conditions, including preexcitation syndrome (PES). Intravenous adenosine is a sensitive and specific means of exposing inapparent pathways in such patients. Yet, it may not be sensitive when complete atrioventricular (AV) block is not achieved because a low dose of adenosine is used. We evaluated the yield of a high-dose adenosine test that achieved complete AV nodal block for unmasking inapparent pathway in a healthy population.

Methods: We retrospectively reviewed all Israeli air force (IAF) academy candidates who were referred to adenosine test based on a cardiologist's suspicion of PES. The results of the adenosine test were recorded, including the adenosine dose required to achieve complete AV block. The medical records of the subjects were reviewed to identify any adverse cardiovascular outcome.

Results: Fifty-nine subjects who underwent adenosine test were followed for 35.42 ± 24 months. Complete AV block was achieved in all subjects with an average adenosine dose of 22.51 ± 12.67 mg. None of the subjects had evidence of an inapparent pathway. All subjects completed military service without adverse outcomes.

Conclusions: The vast majority of young patients with a short PR interval do not have evidence of an accessory pathway and have a favorable prognosis. Thus, the yield of adenosine test in young combat recruits is questionable. Yet, if there is no evidence of an accessory pathway while achieving complete AV block on adenosine test, the chance of an accessory pathway being present is probably extremely low.

Ann Noninvasive Electrocardiol 2011;16(2):180–183

adenosine; military recruits; preexcitation; WPW

Cardiovascular evaluation is a crucial part of the screening process of athletes and military recruits. This evaluation includes, in addition to a meticulous medical history and physical examination, a resting electrocardiogram (ECG). The resting ECG may reveal abnormalities such as long QT and Brugada syndromes and preexcitation syndrome (PES), which may result in sudden death. The presence of PES even in asymptomatic subjects may rarely lead to sudden death and, therefore, it is recommended that electrophysiological studies (EPS) and eventually radiofrequency ablation (RFA) be performed in these subjects before engaging in strenuous physical activity.^{3–11} Yet, in some subjects with PES, the typical signs of preexcitation may be subtle on resting ECG or be absent at all (inapparent accessory pathway) because the conduc-

tion time through the atrioventricular (AV) node is shorter than over an accessory pathway.¹ These cases present a challenge to the clinician, particularly when faced with a decision whether to allow participation in sports or military duties. In these cases, a noninvasive method for the diagnosis of an accessory pathway seems more appropriate than EPS.

Adenosine is widely used to treat reentry tachycardia involving the AV node because of its rapid onset and brief duration of action when given as an intravenous bolus.² Adenosine can transiently inhibit conduction through the AV node during sinus rhythm, but usually does not slow conduction through an accessory pathway and may help in the unmasking of an inapparent accessory pathway. Administration of incremental doses of

Address for correspondence: Alon Grossman, Israeli Air Force Aeromedical Center, Tel Hashomer, Israel E-mail: alon2206@012.net.il

adenosine until AV block is achieved was shown to be 100% sensitive and 100% specific for the detection of inapparent preexcitation in patients with a history of supraventricular tachycardia and a normal ECG during sinus rhythm.³ Use of adenosine test has been proposed for unmasking latent preexcitation to prevent sudden cardiac death in patients with a history of supraventricular tachycardia or for the assessment of family members of subjects with Wolff-Parkinson-White (WPW) syndrome.⁴

Flight academy candidates in the Israeli air force (IAF) are screened for cardiovascular conditions with a resting ECG. When baseline resting ECG revealed short PR interval without a prominent delta wave, subjects were referred to an adenosine test to rule out the presence of an inapparent accessory pathway. To evaluate the yield of a high-dose adenosine test in unmasking inapparent pathway and predicting worse outcome in a healthy population, we summarized our long-term follow-up of subjects in whom the test was performed.

METHODS

The study population included male aircrew candidates evaluated at the IAF aeromedical center in the years 2000–2009. All subjects underwent preliminary evaluation prior to their examination at our facility and none had a significant medical problem. All subjects responded to a questionnaire, in which they were required to report cases of sudden death in first-degree relatives and any cardiac symptoms, including chest pain, palpitations, dyspnea, exercise intolerance, or syncope. Subjects who had a positive response to any of these questions were excluded from the study. All subjects underwent a meticulous physical examination including blood pressure measurement and complete cardiac examination. Following these tests, a resting ECG was performed and interpreted by a cardiologist. Based on ECG findings, subjects were referred to an adenosine test. The test was performed by injecting incremental doses of adenosine until AV nodal block was achieved. The injected adenosine dose was recorded, and the presence of an accessory pathway was evaluated by the examiner based on signs of preexcitation on surface ECG. Side effects were documented by the examiner. In many patients, additional tests such as echocardiography, exercise test, and 24-hour Holter monitoring were performed.

Subjects' records were available for their military service and were evaluated by the study researchers for the occurrence of any cardiac symptoms or episodes of arrhythmias during the follow-up. Continuous variables are expressed as mean $\pm$ SD.

RESULTS

Subjects

Fifty-nine male subjects were referred to adenosine test based on resting ECG findings. Average age at referral was 17.61 years. Blood pressure ($125.03 \pm 13.3/72.54 \pm 8.7$ mm Hg) and pulse ($70.37 \pm 13.1/\text{min}$) were within normal limits in all subjects. All subjects were followed through their computerized clinical records. Median follow-up time was 35 ± 24 months during which most subjects engaged in an active and physically demanding military service.

Baseline ECG and Ancillary Findings

ECG findings that led to the referral to the adenosine test are presented in Table 1. The most common findings were a short PR interval and a suspected delta wave. Among those who had echocardiography ($n = 36$), in two subjects minimal tricuspid regurgitation was reported, and in one subject, mild pulmonary hypertension was reported. Among those who underwent exercise test ($n = 29$), 5 subjects had short PR during exercise. Twenty-seven subjects underwent 24-hour Holter monitoring and almost all had atrial and/or ventricular premature beats. The additional tests did not contribute to the diagnosis.

Adenosine Test

Complete AV block was achieved in all subjects referred to adenosine testing. Average adenosine dose required for achievement of complete AV block was 22.5 ± 12.7 mg. Complete AV block

Table 1. Resting ECG Findings

PR interval (seconds)	0.11 ± 0.008
Short PR/normal PR	48/11
Suspected delta wave/absent delta wave	15/44
ICRBBB (number of subjects)	15
ST-T segment changes (number of subjects)	3

was achieved in most subjects with a dose of 18 mg of adenosine (37 subjects) while the maximal dose required was 80 mg (one subject). None of the subjects had ECG findings compatible with an inapparent pathway. No adverse outcomes were noted during the test, although most subjects reported flushing.

Follow-up

None of the subjects had any complaints of palpitations, chest pain, or dyspnea during the service. No arrhythmias were recorded during the follow-up period.

DISCUSSION

Identification of the PES in asymptomatic athletes and military candidates may be extremely difficult in subjects with minimal or no evidence of preexcitation on resting ECG. Because of the potential for sudden death in subjects with PES, particularly during physical exertion, efforts must be made to diagnose this condition and offer definitive treatment or prohibit participation in competitive sports or military activity. Because a high index of suspicion is required to make the diagnosis of PES, it seems logical that even subjects with minimal resting ECG findings such as an isolated short PR be referred for further evaluation, even in the absence of symptoms. The prevalence of preexcitation pattern in 19,734 consecutive ECGs obtained was reported at 0.2%.⁶ The yearly incidence of newly diagnosed cases of WPW in the general population is substantially lower at 0.04%, 50% of whom will be asymptomatic.⁷ Therefore, it may be extrapolated from both these studies that only one of five subjects with a suspicious ECG will indeed have WPW and only one of 10 will develop symptoms. Thus, performance of invasive procedures, such as EPS, in these subjects seems inappropriate as they expose the subject to a procedure with potential complications based on minimal clinical suspicion and the chance of identifying true disease is relatively low. In such situations, a noninvasive test with minimal complications, such as the adenosine test is more appropriate and may be more acceptable to the subjects' being evaluated.

The use of the adenosine test for asymptomatic subjects has not been extensively studied,^{4-8,9} yet, we believe that because of its high sensitivity it is appropriate as an alternative for inva-

sive procedures in certain clinical situations, such as in the screening of family members or among sports or military candidates with subtle signs of PES.

In our series of young healthy subjects, atrioventricular nodal (AVN) block was achieved in all subjects. Previous studies limited the use of adenosine to a fixed dose, and, therefore, failed to achieve AVN block in some subjects.¹ The adenosine test has 100% sensitivity and 100% specificity only when AVN block is achieved. Since no significant side effects were noted in our series despite the high doses of adenosine used in some of the subjects, we believe that the test should be performed until AVN block is achieved or until side effects develop, and should not be limited by a prespecified adenosine dose.

The lack of positive test in our series is not surprising, since all subjects were asymptomatic and ECG findings were minimal in most of them. Yet, the high sensitivity of the test made it possible to allow those with a negative test to participate in flight training without limitations. The fact that none of the subjects in whom an accessory pathway was excluded developed any cardiac symptoms or arrhythmias during the follow-up period further substantiates the use of this test as a non-invasive alternative to EPS.

We did not identify any subject with an inapparent accessory pathway and none of the subjects reported any adverse cardiovascular outcomes during the follow-up period. This may raise the question whether adenosine test is cost-effective in young healthy asymptomatic subjects with borderline ECG findings before recruitment to the army. A larger long-term study is required to answer this question.

The major limitation of this study is the fact that the subjects did not undergo EPS as a definitive method to rule out an inapparent pathway. Yet, as previous studies documented a good correlation between EPS results and adenosine test,²⁻¹⁰ we believe that it may be relied upon as a noninvasive alternative to EPS in a population such as the one in our study.

We do not recommend performing adenosine test in all asymptomatic subjects with ECG signs compatible with WPW syndrome. Yet, we believe that it should be performed in situations, in which WPW syndrome must be ruled out with a degree of certainty such as in elite athletes or aviators.

CONCLUSIONS

The adenosine test is a reliable noninvasive alternative to EPS in asymptomatic subjects with suspected signs of preexcitation on resting ECG. If AVN block is achieved and no dual physiology is noted, the natural history of these subjects is favorable and it seems that these subjects may participate in competitive sports and engage in intense military activities. Larger series and a longer follow-up period are required to further substantiate these results.

REFERENCES

1. Garratt CJ, Antoniou A, Griffith MJ, et al. Use of intravenous adenosine in sinus rhythm as a diagnostic test for latent pre-excitation. *Am J Cardiol* 1990;65(13):868–873.
2. Malcolm AD, Garratt CJ, Camm AJ. The therapeutic and diagnostic cardiac electrophysiological uses of adenosine. *Cardiovasc Drugs Ther* 1993;7:139–147.
3. Pappone C, Radinovic A, Santinelli V. Sudden death and ventricular pre-excitation: Is it necessary to treat the asymptomatic patients? *Curr Pharm Des* 2008;14(8):762–765.
4. Viskin S, Fish R, Glick A, et al. The adenosine triphosphate test: A bedside diagnostic tool for identifying the mechanism for supraventricular tachycardia in patients with palpitations. *J Am Coll Cardiol* 2001;38(1):173–177.
5. Santinelli V, Radinovic A, Manguso F, et al. Asymptomatic ventricular pre-excitation: A long term prospective follow-up of 293 adult patients. *Circ Arrhythm Electrophysiol* 2009;2(2):102–107, pp. 7–120.
6. Ferrer MF. Electrocardiographic variations, arrhythmias, pacemakers. In: Lew EA, Gajewski J. (eds.): *Medical Risks: Trends in Mortality by Age and Time Elapsed*. New York, Praeger, 1990.
7. Munger TM, Packer DL, Hammil SC, et al. A population-study of the natural history of Wolff-Parkinson-White syndrome in Olmsted county Minnesota 1953-1989. *Circulation* 2000;101(13):1568–1577.
8. Belhassen B, Fish R, Viskin S, et al. Adenosine-5'-Triphosphate test for the noninvasive diagnosis of concealed accessory pathway. *J Am Coll Cardiol* 2000;36:803–810.
9. Sen-Chowdhry S, McKenna WJ. Sudden cardiac death in the young: A strategy for prevention by targeted evaluation. *Cardiology* 2006;105:196–206.
10. Belhassen B, Fish R, Glikson M, et al. Noninvasive diagnosis of dual AV node physiology in patients with AV nodal reentrant tachycardia by administration of Adenosine-5'-Triphosphate during sinus rhythm. *Circulation* 1998;98:47–53.
11. Santinelli V, Radinovic A, Manguso F, et al. The natural history of asymptomatic ventricular pre-excitation a long term prospective follow-up study of 184 asymptomatic children. *J Am Coll Cardiol* 2009;53(3):275–280.