ADENOSINE STRESS PROTOCOLS FOR NUCLEAR CARDIOLOGY IMAGING

Baskot Branislav,1 Obradovic Slobodan,2 Rafajlovski Saso,2 Gligic Branko,2 Orozovic Vjekoslav,2 Ratkovic Nenad,2 Ristic-Angelkov Andjelka,2 Jung Robert,3 Ivanovic Vladimir,3 Bikicki Miroslav,3 Pavlovic Miodrag4

1Nuclear Medicine Institute, Military Medical Academy, Belgrade, Serbia
2Intensive Care Clinic, Military Medical Academy, Belgrade, Serbia
3Institute for Cardiovascular Disease, Sremska Kamenica, Serbia
4Cardiology Department, Medical Centre, Apatin, Serbia

Abstract: The treadmill test combined with myocardial perfusion imaging (MPI) is a commonly used technique in the assessment of coronary artery disease (CAD). However, there is a group of patients who may not be able to undergo the treadmill test. Pharmacologic stress testing is increasingly utilized for stress perfusion imaging and currently accounts for nearly 40% of all nuclear stress testing [8]. The aim of this study was the introduction of adenosine stress protocols in our nuclear laboratory, and the following, recording and comparing of the frequency and severity of side-effects.

Methods: We performed two kinds of adenosine stress protocols on 186 patients who underwent MPI with radiotracer 99mTc-sestamibi: 1st: 47 patients underwent AdenoSCAN abbreviated protocol IV. adenosin 140 μg/kg/min for 3 minutes; 2nd: AdenoEX combined with low level 50W bicycle exercise in 139 patients. We followed and compared side-effects (minor and major events) between AdenoSCAN and AdenoEX protocol, and established an adequate time for imaging of both protocols.

Results: Compared with AdenoSCAN, AdenoEX protocol was tolerated by all patients; it reduced all side-effects and improved image quality. Using AdenoEX protocol we found that the heart-to-liver ratio was significantly better, and we established a time of imaging of 15 minutes after stress, compared to the AdenoSCAN time of imaging which was a minimum of 45 minutes after stress.
Conclusion: This study gives advantages to AdenoEX protocol, because it had fewer side-effects, improved patients' tolerance, improved image quality, and enhanced efficiency and throughput given the opportunity for earlier imaging.

Key words: Myocardial perfusion imaging, Adenosine, Adenosine stress protocols

Introduction

An estimated 2.8 million pharmacologic studies were performed in the United States in 2001, including 1.4 million with adenosine [2, 3, 4, 8]. Adenosine is an endogenous purine nucleotide, which slows atrioventricular conduction and dilates coronary and peripheral vessels. Adenosine is produced intracellularly, in vascular smooth muscle and endothelial cells from adenosine triphosphate or S-adenosyl methionine pathways. There are several types of adenosine receptors. The A2 receptor, located in vascular cells, is divided into two types; a and b. The A2a receptor predominantly mediates coronary arterial vasodilatation, the A2b receptor produces vasodilatation in most vascular beds except the renal afferent arterioles and hepatic veins where it causes vasoconstriction. The A1 receptor is located in the cardiac myocytes and its activation causes negative dromotropic effects, atrioventricular (AV) block, tachypnea, and chest pain. The A2b and A3 receptors are likely to be responsible for bronchospasm [1, 2, 3, 6, 8].

Adenosine has a very short half-life of less than 2 seconds and a rapid onset of action. It induces its peak hyperemic effect within 2 minutes (84 ± 46 seconds, range 23–125 seconds) of infusion and returns to baseline within 2 minutes (145 ± 67 seconds, range 54–310 seconds) after termination of the infusion [13, 14]. The radiotracer for MPI must therefore be administrated during the infusion.

Material and Methods

A total of the 186 (125 males, age range 24–74, 61 females, age range 28–78) patients who underwent MPI with radiotracer ⁹⁹mTc-sestamibi were included in this study. This study included patients who had exercise limitations, a limited capacity for exercise, or contraindication to exercise. We examined patients with medically stable chest pain (or anginal equivalent), symptoms for the evaluation of suspected cardiac ischaemia, with prior coronary disease or myocardial infarction, and follow-up effects of therapy percutaneous coronary intervention (PCI), and by-pass surgery (ACB). In all patients we performed two kinds of adenosine stress protocols; in 47 of them (21 males, age range 65 to 74, 26 females, age range 61 to 78) we used adenosine – AdenoSCAN abbreviation protocol – and in 139 (104 male, 35 female) adenosine in combination with low level bicycle exercise 50 W – AdenoEX.
Adenosine stress protocols:

1. **Abbreviated AdenoSCAN protocol** when we administrated adenosine by IV. infusion 140 μg/kg/min during 3 minutes. Radiotracer $^{99m}$Tc-sestamibi, was administrated during the infusion at the end of the 2nd minute (Fig. 1).

Radiopharmaceutical (99mTc–sestamibi)

![Figure 1 – AdenoSCAN abbreviated protocol](image1)

(140μg/kg/min IV. infusion

2. **AdenoEX protocol** – we administered adenosine in a dose of 140 μg/kg/min in combination with supine low level bicycle exercise 50 W. We started with the infusion at the end of the 1st minute of bicycle exercise, and finished in the 5th minute. The bicycle exercise continued for one minute more to the end of 6th minute. Radiotracer $^{99m}$Tc-sestamibi was administrated during the adenosine infusion at the end of the 2nd minute (Fig. 2).

![Figure 2 – AdenoSCAN protocol 6 minute adenosine IV 140 μg/kg/min (a); AdenoEX protocol 4 minute adenosine IV 140μg/kg/min with adjunctive low level exercise 50 W (b)](image2)

283
During both kinds of protocols we followed these procedures: We recorded blood pressures (BP); heart rate (BPM) ECG on the monitor, recorded occurrence of symptoms (chest pain, nausea, dyspnea, etc.); marked the clock time of the injection of radiotracer relative to the start and the end of the adenosine infusion; after injection of the radiotracer, the infusion continued for 2 minutes; the patient continued with exercise (AdenoEX) for 1 minute after the infusion stopped. We monitored BP, BPM and ECG for the next 5 minutes after the completion of the infusion, continuing clinical monitoring if chest pain or significant ECG changes persisted [9, 10, 11, 12].

We started imaging 15 minutes for AdenoEX, and 45 minutes for AdenoSCAN, after the radiotracer was injected.

Results

We compared side-effects using various pharmacologic agents in our laboratory for the pharmacologic stress tests and concluded: In our group non-cardiac side-effects occurred in 50% of the patients who were receiving dipyridamole, and almost 80% of the patients receiving adenosine. Use of aminophylline for the reversal of side-effects was required in less than 4% of the patients receiving dipyridamole and by none receiving adenosine. We founded side-effects were more common with adenosine than dipyridamole, but they were short-lived and well tolerated. AV block (1st and 2nd degree) occurred in less than 4% of patients, and it was usually in the first 2 minutes of adenosine infusion and was transient. The most common side-effects with adenosine were chest pain 23%, flushing 39%, dyspnea 31% and gastrointestinal discomfort 12%. The most common side-effects with Dobutamine were chest pain 34%, flushing 8%, dyspnea 6%, ST changes 23%, and arrhythmias up to 49%, when the test must be interrupted. Ventricular arrhythmias occurred more frequently in patients with LV dysfunction, fixed perfusion defects, or wall motion abnormality in the rest (Table 1).

Table 1 – Таблица 1

<table>
<thead>
<tr>
<th>Side-effects</th>
<th>ADENOSINE ( n = 186 )</th>
<th>DIPYRIDAMOLE ( n = 764 )</th>
<th>DOBUTAMINE ( n = 98 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest Pain</td>
<td>23%</td>
<td>18%</td>
<td>34%</td>
</tr>
<tr>
<td>Flushing</td>
<td>39%</td>
<td>26%</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>31%</td>
<td>2%</td>
<td>8%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8%</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>GI discomfort</td>
<td>8%</td>
<td>7%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Adenosine stress protocols for Nuclear Cardiology imaging

### Side-effects

<table>
<thead>
<tr>
<th>Side-effects</th>
<th>Adenosine (n = 186)</th>
<th>Dipyridamole (n = 764)</th>
<th>Dobutamine (n = 98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>7%</td>
<td>18%</td>
<td>6%</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>2%</td>
<td>5%</td>
<td>49%</td>
</tr>
<tr>
<td>AV block</td>
<td>4%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>ST Δ</td>
<td>5%</td>
<td>9%</td>
<td>23%</td>
</tr>
<tr>
<td>ANY</td>
<td>79%</td>
<td>49%</td>
<td>55–80%</td>
</tr>
</tbody>
</table>

$\text{ST} \Delta = \text{St segment changes on ECG, ANY = any side-effect}$

In this study we compared frequency and severity of side-effects using two kind of adenosine protocols: AdenoSCAN and AdenoEX. AdenoEX markedly reduced side-effects: less hypotension, reduced symptoms like chest pain (11% versus 24%), flushing (15% vs. 41%), dyspnea (12% vs. 35%), fewer noncardiac side-effects (57% vs. 87%), not one AV block occurred and there were no arrhythmias (Table 2). None of the patients had an incidence of severe adverse events (major events): death, myocardial infarction, or bronchospasms.

<table>
<thead>
<tr>
<th>Side-effects</th>
<th>AdenoSCAN (n = 47)</th>
<th>AdenoEX (n = 139)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain</td>
<td>24%</td>
<td>11%</td>
</tr>
<tr>
<td>Flushing</td>
<td>41%</td>
<td>15%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>35%</td>
<td>12%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9%</td>
<td>3%</td>
</tr>
<tr>
<td>GI discomphort</td>
<td>7%</td>
<td>1%</td>
</tr>
<tr>
<td>Headache</td>
<td>8%</td>
<td>3%</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>AV block</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>ST Δ</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>ANY</td>
<td>87%</td>
<td>57%</td>
</tr>
</tbody>
</table>

$\text{ST} \Delta = \text{St segment changes on ECG, ANY = any side-effect}$

When we combined adenosine with low level exercise, the adenosine’s vasodilatation of the splanchnic bed was partially counteracted by the vasoconstriction of this bed because of the exercise-induced cateholamine increase. That resulted in an improvement of the cardiac image quality (Fig. 3). We were improving the heart-to-liver (target-background) ratio and that is extremely important for the radiopharmaceutical we used ($^{99m}\text{Tc}$-sestamibi), because it was cleared primarily by the hepatobiliary tract. We standardized the time for ima-
ging with AdenoEX, and we performed imaging 15 minutes after \(^{99m}\text{Tc}\)-sesta-mibi injections, compared with 45 minutes for the AdenoSCAN protocol.

![Figure 3 - Myocardial perfusion imaging](image)

Panel a demonstrates similar intensity in the liver as noted in the myocardium following an adenosine infusion. When low level exercise is combined with adenosine infusion (b), much less hepatic activity is present when compared with the myocardium.

**Discussion**

There are many patients who may not be able to perform adequate exercise due to certain clinical, physical or physiological conditions. Pharmacologic stress combined with MPI is an effective tool for the management (diagnosis, risk stratification, treatment and follow-up) of patients with CAD, and becomes an especially indispensable tool in the elderly. Using a vasodilator (adenosine, dipyridamole) for pharmacologic stress we altered the myocardial blood flow through the coronary arteries and caused differential dilatation of the normal and stenosed arteries [5, 6, 7, 8]. We had a high incidence of side-effects, but these tended to last for a few minutes and rarely required medical intervention. When we added exercise to adenosine stress, patients' tolerance was shown to improve. In Elliot et al. [11], patients were asked to rate the intensity and frequency of their side-effects during AdenoSCAN compared with AdenoEX. Side-effects were measured on the symptom severity score. The score averaged 15.5 with the AdenoSCAN and only 4.5 using the AdenoEX protocol. The number of side-effects occurring per patient was also greater with AdenoSCAN than AdenoEX (2.7 vs. 1.4). When adenosine stress is combined with exercise, adenosine's vasodilatation of the splanchnic bed should be at least partially contracted by the vasoconstriction of this bed because of the
exercise-induced cateholamine increase [8, 10, 11]. The result should be an improvement in cardiac image quality, because that improves the heart-to-background ratio and that is most the important for the radotracers cleared primarily by the hepatobiliary tract (99mTc-sestaminbi and tetrofosmin). Image quality was compared in 3 AdenoEX studies and showed that the heart-liver ratio was significantly better with AdenoEX than with AdenoSCAN [11, 12, 13].

**Conclusion**

Combining exercise with adenosine infusion (AdenoEX) we had advantages that included absence of arrhythmia, AV block, and hypotensive side-effects. We improved patient tolerance with the implication of greater patient acceptance, improved image quality, enhanced efficiency and throughput, given the opportunity for earlier imaging. We documented the safety of the AdenoEX protocol.

**REFERENCES**


Резиме

ПРОТОКОЛИ НА АДЕНОЗИН-СТРЕС ЗА НУКЛЕАРНА КАРДИОЛОШКА ВИЗУЕЛИЗАЦИЈА

Башкот Бранислав,1 Обрадовиќ Слободан,2 Рашајовски Сашо,2 Глигиќ Бранко,2 Орозовиќ Вјекослав, Ратковиќ Ненад,2 Ристиќ-Анѓелков Анѓелка,2 Јунг Роберт,3 Ивановиќ Владимир,3 Бикицки Мирослав,4 Павловић Милорад4

1Институт за нукларна медицина, Воено-медицинска академија, Белград, Србија
2Клиника за интензивна нега, Воено-медицинска академија, Белград, Србија
3Институт за кардiovаскуларни болести, Сремска Каменица, Србија
4Оддел за кардиолошта, Медицински центар, Апатин, Србија

Апстракт: Тредмил-тестот комбиниран со визуелизација на миокардна перфузија е техника што вообичаено се користи за оценување на болеста на коро-

нарните артерије. Сепак, има група пацијенти што не можат да бидат подложени на тредмил-тестот. Фармаколошкото тестирање за стрес сè повеќе се користи за визуелизацијата на перфузијата и моментално се применува во близу 40% од сите нуклеарни тестирања на стресот. Целта на оваа студија е воведувањето на протоколите за аденоzin-стрес во нашата нуклеарна лабораторија и следењето, запишувањето и споредувањето на зачестеноста и интензитетот на придружните појави.

Методи: Ние изведовме два вида протоколи на аденоzin-стрес на 186 пациенти кои беа подложени на визуелизација на миокардната перфузија со радио трејсер 99mTc-sestamibi: 1. 47 пациенти без подложени 3 минути на скратен протокол AdenoSCAN IV аденоzin 140μg/kg/min; 2. AdenoEX комбиниран со ниско ниво на 50W вежба на велосипед кај 139 пациенти. Ги следевме и ги споредуваме придружните појави (помали и поголеми) меѓу протоколите AdenoSCAN и AdenoEX и констатирале соодветно време за визуелизација на двета протокола.

Резултати: Во споредба со AdenoSCAN, протоколот AdenoEX беше толериран од сите пациенти; тој ги намале сите придружни појави и го подобри квалитетот на визуелизацијата. Користејќи го протоколот AdenoEX утврдивме дека односот срце кон црн дроб беше значително подобар и утврдивме време на визуелизација од 15 минути по стресот, во споредба со времето на визуелизација на AdenoSCAN, кое беше минимално 45 минути по стресот.

Заключок: Ова проучување му дава предност на протоколот AdenoEX, бидејќи имаше помалку придружни ефекти, подобрена толеранција на пациентите, подобрен квалитет на раната визуелизација и засилена ефикасност и капацитет.

Ключни зборови: визуелизација на миокардиска перфузија, аденоzin, протоколи на аденоzin-стрес

Corresponding Author:

Baskot Branislav,
Nuclear Medicine Institute,
Military Medical Academy,
Belgrade, Serbia

E-mail: baskotbranislav@yahoo.com