

ADENOSINE STRESS PROTOCOLS FOR NUCLEAR CARDIOLOGY IMAGING

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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 ^{99m}Tc-sestamibi: **1st:** 47 patients underwent AdenoSCAN abbreviated protocol IV. adenosin 140µg/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 A_{2a} receptor predominantly mediates coronary arteriolar vasodilatation, the A_{2b} 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 A_{2b} 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 administered 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 ^{99m}Tc-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 $\mu\text{g}/\text{kg}/\text{min}$ during 3 minutes. Radiotracer $^{99\text{m}}\text{Tc}$ -sestamibi, was administrated during the infusion at the end of the 2nd minute (Fig. 1).

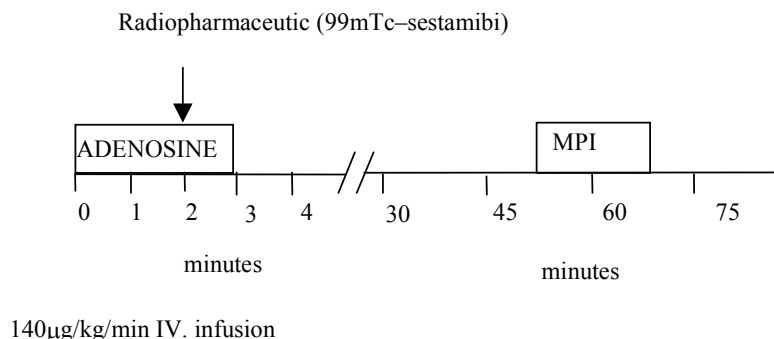


Figure 1 – AdenoSCAN abbreviated protocol
Слика 1 – Скусен протокол на AdenoSCAN

2. **AdenoEX protocol** – we administered adenosine in a dose of 140 $\mu\text{g}/\text{kg}/\text{min}$ 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 $^{99\text{m}}\text{Tc}$ -sestamibi was administered during the adenosine infusion at the end of the 2nd minute (Fig. 2).

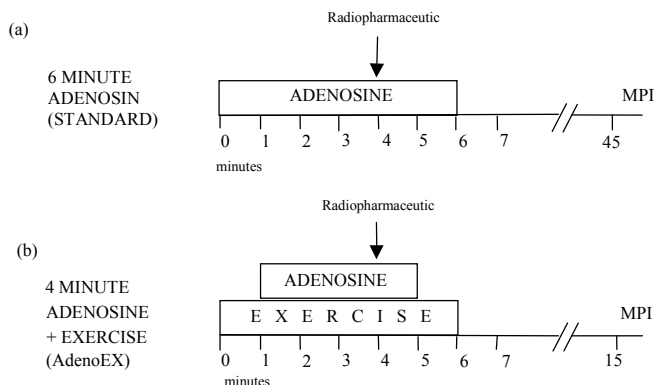


Figure 2 – AdenoSCAN protocol 6 minute adenosine IV 140 $\mu\text{g}/\text{kg}/\text{min}$ (a); AdenoEX protocol 4 minute adenosine IV 140 $\mu\text{g}/\text{kg}/\text{min}$ with adjunctive low level exercise 50 W (b)
Слика 2 – Протокол на AdenoSCAN 6 минути аденозин IV 140 mg/kg/min (a), AdenoEX протокол 4 минути аденозин IV 140 mg/kg/min со дополнителни со ниско ниво вежби 50W (b)

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 raditracer, 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%, dyspnea 8%, 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 – Табела 1

Pharmacologic Stress testing – side-effects
Фармаколошко тестирање на стрес – споредни ефекти

<i>Side-effects</i>	ADENOSINE n = 186	DIPYRIDAMOLE n = 764	DOBUTAMINE n = 98
Chest Pain	23%	18%	34%
Flushing	39%	26%	< 1 %
Dyspnea	31%	2%	8%
Dizziness	8%	6%	3%
GI discomfort	8%	7%	3%

<i>Side-effects</i>	ADENOSINE n = 186	DIPYRIDAMOLE n = 764	DOBUTAMINE n = 98
Headache	7%	18%	6%
Arrhythmia	2%	5%	49%
AV block	4%	0%	0%
ST Δ	5%	9%	23%
ANY	79%	49%	55–80%

STΔ = 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 2 – Табела 2

Comparing severity and frequency of side-effects with AdenoSCAN versus AdenoEX
Споредна сила и фреквенција на споредни ефекти со аденоСКЕН
наспроти AdenoEX

<i>Side-effects</i>	AdenoSCAN n = 47	AdenoEX n = 139
Chest pain	24%	11%
Flushing	41%	15%
Dispnea	35%	12%
Dizziness	9%	3%
GI discomphort	7%	1%
Headache	8%	3%
Arrhythmia	2%	0%
AV block	3%	0%
ST Δ	4%	1%
ANY	87%	57%

STΔ = 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 catecholamine 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}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}Tc -sestamibi injections, compared with 45 minutes for the AdenoSCAN protocol.

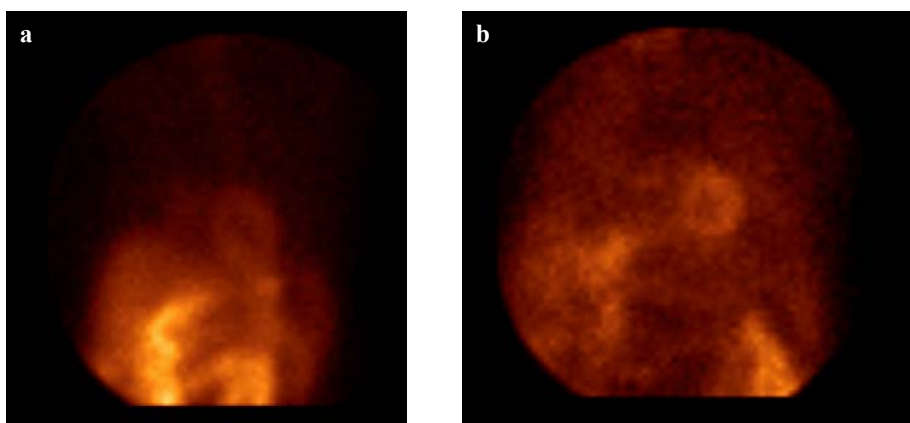


Figure 3 – Myocardial perfusion imaging; **a.** AdenoSCAN versus **b.** AdenoEX
Слика 3 – Приказ на миокардна перфузија **а.** AdenoSCAN versus **б.** AdenoEX

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 counteracted by the vasoconstriction of this bed because of the

exercise-induced catecholamine 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 radiotracers cleared primarily by the hepatobiliary tract (^{99m}Tc -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

1. Baskot Branislav (2006): NUCLEAR CARDIOLOGY, SPECT Myocardial Perfusion Scintigraphy – *determinaion of culprit lesion*. Andrejevic foundation Držičeva 11. 11116 Belgrade.
2. Doglas Miller D. (2006): Chapter 4 Pharmacologic stressors in coronary artery disease. Vasken Dilsizian, Jagat Narula, Eugene Braunwald: *Atlas of Nuclear Cardiology* second edition. Current medicine LLC, 400 Market street, Suite 700 Philadelphia, PA 19106.
3. Gopinath G., Buscombe J.R. (2004): Pharmacological stress agents in Nuclear Cardiology. *World Jour. of Nuclear Medicine*, Vol 3, number 1 (64–71). January
4. Gregory S., Thomas, Michael I. Miyamoto (2004): Should Simultaneous Exercise Become the Standard for Adenosine Myocardial Perfusion Imagigng. *Excerpta Medica*; 3D–11D.
5. Leslee J., Shaw, Robert Hendel, Salvador Burges-Neto, Michael S., Lauer, Naomi Alazraki, Joy Burnette, Elizabeth Karwczynska, Manuel Cerqueira, Jamsid Maddahi (2003): Prognostic value of Normal Exercise and Adenosine ^{99m}Tc -tetrofosmin SPECT imaging: results from the Multicenter Registry of 4.728 Patients. *Journal of Nuclear Medicine*; vol. 44 No 2 (134–139).
6. Frans J.Th. Wackers, Wendy Bruni, Barry L. Zaret (2004): *Nuclear Cardiology: The basics* – How to set Up and Maintain a Laboratory. chapter 5 Stress procedures 43–60. Humana Press 999 Riverview Drive, Suite 208 Totowa, New Jersey; 07512.
7. Kyuong Ah Chun, Jaetae Lee, Sang-Woo lee, Byeong-Cheol Ahn, Jeoung-Hee Ha, Ihn Ho Cho, Shung Chull Chae, Kyu Bo Lee (2006): Direct comparison of adenosine and adenosine 5'-triphosphate as pharmacologic stress agents in conjunction with Tl-201 SPECT: Hemodynamic response, myocardial tracer uptake, and size of

perfusion defects in the same subjects. *Journal of Nuclear Cardiology*; Vol 13, No 5 (621–29) September/October.

8. Gilbert J. Zoghbi, Ami E. Iskandrian (2005): Chapter 14 Coronary Artery Disease detection: Pharmacologic Stress 233–53. *Clinical Nuclear Cardiology - State of the art and future directions* 3rd edition. Elsevier Mosby The Curtis Centre, 170 S Independence Mall W 300E. Philadelphia, Pennsylvania 19106.

9. Garry V. Heller, Robert C. Hendel (2004): *Nuclear Cardiology – practical applications*, Chapter 9 Performing the test: Exercise and Pharmacologic Stress Test. 119–33.

10. Rory Hachamovitch, Daniel S. Berman (2005): Chapter 16 Prognostic value of Pharmacologic Stress Myocardial Perfusion Scintigraphy and its Use in Risk Stratification 265–80. *Clinical Nuclear Cardiology – State of the art and future directions* 3rd edition. Elsevier Mosby The Curtis Centre, 170 S Independence Mall W 300E. Philadelphia, Pennsylvania 19106.

11. Elliot MD., Holly TA., Leonard SM., Hendel RC. (2000): Impact of an abbreviated adenosine protocol incorporating adjunctive treadmill exercise on adverse effects and image quality in patients undergoing stress myocardial perfusion imaging. *J Nucl Cardiol*; 7: 584–589.

12. Thomas GS., Miyamoto MI., Morello AP., Majmundar H., Thomas H., Sampson CH., Hachamovitch R., Shaw LJ. (2004): Technetium-99m based myocardial perfusion imaging predicts clinical outcome in the community outpatient setting: the Nuclear Utility in the Community (NUC) study. *J Am Col Cardiol*; 43: 213–223.

13. Samady H., Wackers FJT., Joska TM., Zaret BL., Jain D. (2002): Pharmacologic stress perfusion imaging with adenosine; role of simultaneous low-level treadmill exercise. *J Nucl Cardiol*; 9: 188–196.

14. Sabahat Bokhari, Edvard P. Ficaro, Benjamin D. McCallister (2007): Adenosine stress protocols for myocardial perfusion imaging. *J Nucl Cardiol*; 14: 415–6.

Резиме

ПРОТОКОЛИ НА АДЕНОЗИН-СТРЕС ЗА НУКЛЕАРНА КАРДИОЛОШКА ВИЗУЕЛИЗАЦИЈА

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

нарните артерии. Сепак, има група пациенти 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 аденозин-стрес во нашата нуклеарна лабораторија и следењето, запишувањето и споредувањето на зачестеноста и интензитетот на придружните појави.

Методи: Ние изведовме два вида протоколи на аденозин-стрес на 186 пациенти кои беа подложени на визуелизација на миокардната перфузија со радио трепсер ^{99m}Tc -sestamibi: 1. 47 пациенти без подложени 3 минути на скратен протокол AdenoSCAN IV аденозин $140\mu\text{g}/\text{kg}/\text{min}$; 2. AdenoEX комбиниран со ниско ниво на 50W вежба на велосипед кај 139 пациенти. Ги следевме и ги споредувавме придружните појави (помали и поголеми) меѓу протоколите AdenoSCAN и AdenoEX и констатиравме соодветно време за визуелизација на двата протокола.

Резултати: Во споредба со AdenoSCAN, протоколот AdenoEX беше толериран од сите пациенти; тој ги намали 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.

Заклучок: 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.

Клучни зборови: визуелизација на миокардиска перфузија, аденозин, протоколи на аденозин-стрес

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