Arrhythmias in vasodilator stress testing

Rajeeve Subbiah, MD,[a] and Pravin V. Patil, MD[a]

[a] Section of Cardiology, Department of Medicine, Temple University School of Medicine, Philadelphia, PA

Received Jan 4, 2016; accepted Jan 4, 2016
doi:10.1007/s12350-016-0407-5

See related article, pp. 405–409

In this issue, Massalha et al retrospectively analyzed the conduction abnormalities that occurred with dipyridamole infusion.[1] The authors examined 2010 patients, noting that 17.4% of the patients had baseline conduction abnormalities (defined as one fascicular block, bifascicular block, tri-fascicular block, non-specific intraventricular conduction delay (IVCD), atrial flutter or atrial fibrillation). After infusion of dipyridamole, it was noted that 16 patients had transient atrioventricular (AV) conduction changes; this was more pronounced in patients who already had baseline conduction abnormalities (0.3% vs 3.1%, $P < .0001$). While the low incidence of significant conduction abnormalities is reassuring, it is important to recognize the breadth of agents being used in vasodilator stress testing.

"ADENOSINE-LIKE" COMPOUNDS

The first inquiry into the cardiac activity of adenosine-like compounds was performed by Drury and Szent-Gyorgyi in 1929 when they isolated adenosine from bovine hearts and noted its effect, slowing of SA node and AV node conduction in animal models.[2] Other early testing with adenosine and its analogs was performed mostly in Europe and even the early tests showed the conduction effects of adenosine. Wayne et al in 1949 described the effects of adenosine on animals as well as five human subjects, noting that conduction abnormalities were dose dependent as low dose induced sinus tachycardia, but higher doses created SA node and AV node blocks.[3]

Dipyridamole was introduced as a coronary dilator for the treatment of angina in the 1960s and was noted to inhibit the uptake of adenosine into red blood cells.[4] In the 1970s, adenosine was additionally found to be a mediator of coronary blood flow.[5] It was noted that in an ischemic episode myocardial adenosine levels increase dramatically, this eventually led Crea et al to note that adenosine administration had produced chest pain in patients with silent ischemia by exercise testing.[6]

The first vasodilator stress imaging was done in 1978 using dipyridamole.[7] This method was generally considered safe and low risk to patients.[8] Adenosine stress testing followed suit soon after.[9] Although these were considered safe, the possibility of bronchospasm induced from such non-selective adenosine receptor agonists leads to the development of A2A receptor specific agonists, such as regadenoson in the late 1990s.[10,11]

Dipyridamole, adenosine, and regadenoson are currently the most widely used agents for pharmacologic vasodilator stress testing. While dipyridamole traditionally dominated pharmacologic stress testing in and outside of the US, there was a clear shift toward using other agents for reasons of efficiency and side effect profiles. Recent ASNC member survey in the US in 2013 shows that nearly 84% of pharmacologic stress tests done use regadenoson.[12] The survey also demonstrates a significant reduction in the number of dipyridamole stress tests (Figure 1). It is therefore important to assess the pro-arrhythmic effects across the entire class of vasodilator agents.

PRO-ARRHYTHMIC EFFECTS

Adenosine and adenosine-like compounds were initially found to manifest conduction abnormalities,

Reprint requests: Pravin V. Patil, MD, Section of Cardiology, Department of Medicine, Temple University School of Medicine, 9th Floor Parkinson Pavilion, 3401 N. Broad Street, Philadelphia, PA 19140; *pravin.patil@tuhs.temple.edu*

Funding This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.
J Nucl Cardiol 2017;24:410–2.
1071-3581/$34.00

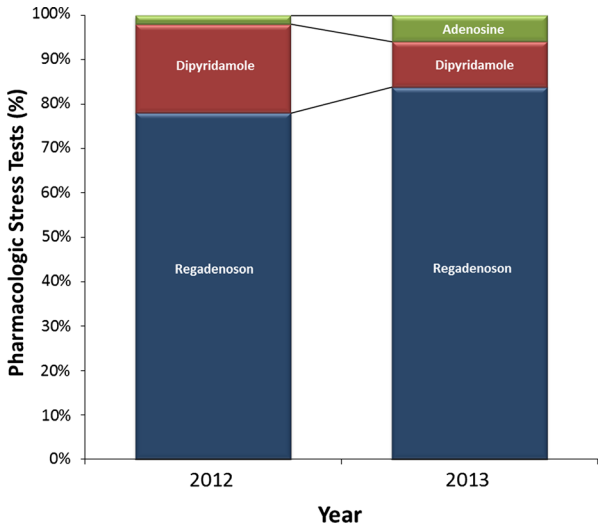

Figure 1. Percentage of pharmacologic stress agent doses. Adapted from the 2013 American Society of Nuclear Cardiology/MedAxiom Nuclear Survey.[12]

and only later found to be acceptable vasodilator agents for stress testing. The cardiology stress protocol and tracers guidelines from the American Society of Nuclear Cardiology (ASNC) note that contraindications to the use of any vasodilator agent include second- or three-degree AV block without a pacemaker or sick sinus syndrome.[13] However, the reported incidence of significant ventricular arrhythmia, tachyarrhythmias, and AV block or symptomatic bradycardia does vary among agents and among study populations (Table 1).

Adenosine is a direct coronary arteriolar vasodilator with non-specific activation of the A2A receptor. Summary data from multiple studies demonstrate an incidence rate of 3%-12% for any type of arrhythmic effect, with varying clinical significance. Registry data show that transient AV nodal block occurs in 7.6% of patients and usually resolves spontaneously. It is evident, however, that patients over 70 years of age have a higher risk of developing AV block. No other serious side effects of adenosine are evident in this registry.[9]

Large-scale studies have also shown that the risk of serious side effects from dipyridamole is low and comparable to those reported in the exercise population.[8] While there have been large studies involving greater than 70,000 patients looking at the safety of dipyridamole, Massalha et al further document the safety of dipyridamole use with a low 0.8% incidence of AV block in 2010 consecutive patients in this issue. Similar to studies with adenosine there were particular at-risk populations worth noting, those with pre-existing AV block.

Regadenoson, the latest generation specific A2A adenosine receptor agonist that is also a direct coronary arteriolar vasodilator, has rapidly become the vasodilator agent of choice with an acceptable side effect profile and ease-of-use that contributes to lab efficiency.[12] Review of study data shows a low incidence of AV block, approximately 2.8%.[11,16]

SUMMARY

There are several different stress protocols and pharmacologic vasodilator agents utilized in clinical cardiology. Although their side effect profiles and pharmacokinetics vary, the different (dipyridamole, adenosine, and regadenoson) are generally well tolerated with minimal side effects. The rate of clinically significant adverse events and pro-arrhythmic effects are similar and low across the different agents.

Table 1. Summary of studies evaluating the pro-arrhythmic effects of pharmacologic stress agents

	Agent	n	Ventricular extrasystoles (%)	Unspecified arrhythmia (%)	Tachyarrhythmia (%)	AV block (%)
>1000 pts						
Cerqueira et al[9]	Adenosine	9256		3.34		7.63
Sun et al[14]	Adenosine	1168	6.25			6.42
Ranhosky et al[15]	Dipyridamole	3911	5.22		3.25	
Lette et al[8]	Dipyridamole	73,806	0.01			
Massalha et al[1]	Dipyridamole	2010				0.8
Cerqueira et al[16]	Regadenoson	1240				2.82
<1000 pts						
Cerqueira et al[16]	Adenosine	631				8.24
Alkoutami et al[17]	Adenosine	600				12.17
Hendel et al[11]	Regadenoson	26				2.78

Disclosures

The authors report no conflict of interest.

References

1. Massalha S, Reizberg I, Israel O, Kapeliovich M, Sholy H, Koskosi A, et al. Conduction abnormalities during dipyridamole stress testing. J Nucl Cardiol 2015. doi:10.1007/s12350-015-0294-1.
2. Drury AN, Szent-Györgyi A. The physiological activity of adenine compounds with especial reference to their action upon the mammalian heart. J Physiol 1929;68:213-37.
3. Wayne EJ, Goodwin JF, Stoner HB. The effect of adenosine triphosphate on the electrocardiogram of man and animals. Br Heart J 1949;11:55-67.
4. Klabunde RE. Dipyridamole inhibition of adenosine metabolism in human blood. Eur J Pharmacol 1983;93:21-6.
5. Berne RM. The role of adenosine in the regulation of coronary blood flow. Circ Res 1980;47:807-13.
6. Crea F, el-Tamimi H, Vejar M, Kaski JC, Davies G, Maseri A. Adenosine-induced chest pain in patients with silent and painful myocardial ischaemia: Another clue to the importance of generalized defective perception of painful stimuli as a cause of silent ischaemia. Eur Heart J 1988;9:34-9.
7. Albro PC, Gould KL, Westcott RJ, Hamilton GW, Ritchie JL, Williams DL. Noninvasive assessment of coronary stenoses by myocardial imaging during pharmacologic coronary vasodilatation. III. Clinical trial. Am J Cardiol 1978;42:751-60.
8. Lette J, Tatum JL, Fraser S, Miller DD, Waters DD, Heller G, et al. Safety of dipyridamole testing in 73,806 patients: The Multicenter Dipyridamole Safety Study. J Nucl Cardiol 1995;2:3-17.
9. Cerqueira MD, Verani MS, Schwaiger M, Heo J, Iskandrian AS. Safety profile of adenosine stress perfusion imaging: Results from the Adenoscan Multicenter Trial Registry. J Am Coll Cardiol 1994;23:384-9.
10. Udelson JE, Heller GV, Wackers FJ, Chai A, Hinchman D, Coleman PS, et al. Randomized, controlled dose-ranging study of the selective adenosine A2A receptor agonist binodenoson for pharmacological stress as an adjunct to myocardial perfusion imaging. Circulation 2004;109:457-64.
11. Hendel RC, Bateman TM, Cerqueira MD, Iskandrian AE, Leppo JA, Blackburn B, Mahmarian JJ. Initial clinical experience with regadenoson, a novel selective A2A agonist for pharmacologic stress single-photon emission computed tomography myocardial perfusion imaging. J Am Coll Cardiol 2005;46:2069-75.
12. American Society of Nuclear Cardiology/MedAxiom Nuclear Survey. J Nucl Cardiol 2014;21:5-88. doi:10.1007/s12350-014-9862-z.
13. Henzlova MJ, Cerqueira MD, Hansen CL, Taillefer R, Siu-Sun Y. ASNC imaging guidelines for nuclear cardiology procedures: Stress protocols and tracers. J Nucl Cardiol 2009;16:331.
14. Sun H, Tian Y, Zheng L, Pan Q, Xie B. Electrocardiographic profile of adenosine pharmacological stress testing. Exp Ther Med 2015;9:1178-84.
15. Ranhosky A, Kempthorne-Rawson J. The safety of intravenous dipyridamole thallium myocardial perfusion imaging. Intravenous Dipyridamole Thallium Imaging Study Group. Circulation 1990;81:1205-9.
16. Cerqueira MD, Nguyen P, Staehr P, Underwood SR, Iskandrian AE, ADVANCE-MPI Trial Investigators. Effects of age, gender, obesity, and diabetes on the efficacy and safety of the selective A2A agonist regadenoson versus adenosine in myocardial perfusion imaging integrated ADVANCE-MPI trial results. JACC Cardiovasc Imaging 2008;1:307-16. doi:10.1016/j.jcmg.2008.02.003.
17. Alkoutami GS, Reeves WC, Movahed A. The safety of adenosine pharmacologic stress testing in patients with first-degree atrioventricular block in the presence and absence of atrioventricular blocking medications. J Nucl Cardiol 1999;6:495-7.