Adenosine Stress Echocardiography

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14.1 Historical Background

Adenosine stress testing is a procedure in which patients are exposed to intravenous infusion of adenosine with simultaneous monitoring of symptoms, hemodynamic parameters, electrocardiogram, and imaging [1]. It is a second-generation vasodilator adenosinergic stress, evolving from the first-generation prototype dipyridamole stress, which acts through the accumulation of endogenous adenosine [2]: Table 14.1. Perfusion imaging with scintigraphy is the dominant application of adenosine stress. Of the 8.4 million myocardial perfusion studies conducted in the USA in 2006, pharmacological stress was used in 3.7 million tests, including infusion of adenosine in 63%, dipyridamole in 30%, and dobutamine in 7% [3]. Radionuclide scintigraphy [4], positron emission tomography [5], or magnetic resonance imaging [6] can be utilized for myocardial perfusion imaging. The conventional stress echocardiography approach is based on functional imaging, which recognizes regional wall motion abnormalities as a diagnostic criterion and ischemia as the necessary end point [7]. Similarly to what happens with dipyridamole [2], high doses of adenosine are required in this case to have high diagnostic sensitivity [8]. Perfusion imaging is also potentially applicable in the stress echocardiography laboratory with myocardial contrast echocardiography [9] and with greater feasibility with coronary flow velocity imaging [10], which is currently recommended in combination with wall motion during vasodilation stress echocardiography [11]. With adequate dosing, adenosine stress echocardiography therefore also has the potential "to kill two birds with one stone," i.e., to assess wall motion and coronary flow reserve simultaneously in one sitting, with a single stress [12], as it is the currently recognized state-of-the-art standard for dipyridamole stress echocardiography [13], also recommended by the European Association of Echocardiography [11]. The clinical appeal of adenosinergic stress may be further enhanced by third-generation

E. Picano, *Stress Echocardiography*,

Table 14.1 Three generations of adenosinergic stress

	Prototype	First clinical application	Mediator	Stimulated receptors	Half-life
First generation	Dipyridamole	1980	Endogenous adenosine	A1, A2A, A2B, A3	Hours
Second generation	Adenosine	1990	Exogenous adenosine	A1, A2A, A2B, A3	Seconds
Third generation	Regadenoson	2000	Selective adenosine agonist	A2A (A1)	Minutes

adenosinergic stresses, i.e., selective A2A adenosine agonists, such as regadenoson [14]. Regadenoson (CVT-3146, Cardiovascular Therapeutics, Palo Alto, CA, USA) is a short-acting third-generation adenosinergic stress agent currently being evaluated in two phase-3 randomized, double-blind clinical trials enrolling more than 2,000 patients worldwide. The affinity of regadenoson for human adenosine A2A receptors exceeds that for adenosine A1 receptors by more than ninefold, and its affinity for A2B and A3 receptors is minimal. Given its selectivity, this A2A receptor agonist has the potential to increase the safety and tolerability of adenosine stress, especially in asthmatic patients. In fact, adenosine accumulates in inflamed bronchial mucosa under conditions of cell stress and hypoxia, and contributes as a mediator of bronchoconstriction in both acute and chronic asthma, mainly through stimulation of A2B receptors.

14.2 Pharmacology and Pathophysiology

Adenosine is a nucleoside, i.e., a purine-based adenine bound to sugar ribose [15] acting through its specific receptors located on the outer surface of the cell membrane. It is produced inside the cell, so it is diffused, driven by the concentration gradient, to extracellular space to activate its receptors, which can be divided into two major subtypes: (1) A1 inhibitory receptors and (2) A2 stimulatory receptors. The A1 receptors predominate in the myocardium, whereas the A2 receptors are found in the coronary arteries (endothelial and smooth muscle cells). Probably the chemistry signal that induces adenosine synthesis is the oxygen supply/demand ratio via the variation of the potential of phosphorylation. In fact, in case of insufficient oxygen supply, there is a reduction in the potential of phosphorylation and the consequent increment of free AMP in the cytoplasm that is available as a substrate of 5′-nucleotidase [16]. The increment of 5′-nucleotidase determines an increased production of adenosine. A2A receptors play a key role in mediating inappropriate arteriolar vasodilation leading to hyperemia and – in presence of critical coronary stenosis – to subendocardial ischemia for vertical and horizontal steal phenomena and regional wall motion abnormality [2]. The human adenosine A2A receptor gene has been localized on chromosome 22q and several genetic polymorphisms have been identified [17] as

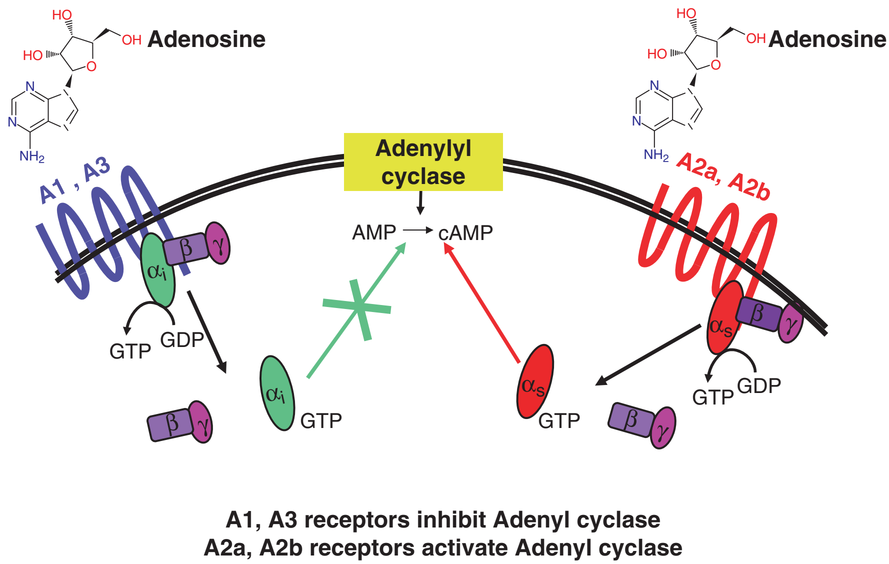

Fig. 14.1 The molecular structure of adenosine receptors

potentially responsible, at least in part, for the heterogeneity in response to coronary flow during stress imaging [18] (Fig. 14.1).

When adenosine binds with phosphate it becomes a nucleotide, i.e., adenosine monophosphate, adenosine diphosphate, and adenosine triphosphate. Actually, one of the pathways of adenosine generation is degradation of those nucleotides, which under normal conditions contribute only up to 10% of the endogenous adenosine in the heart. Approximately 90% of adenosine in the heart is created by the *S*-adenosylhomocysteine hydrolase pathway [4]. A certain amount is also generated by degradation of extracellular AMP. Extracellular adenosine returns into the cell by reuptake through cell membrane by facilitated diffusion, where in a very short time it is degraded by enzyme adenosine deaminase to inosine, which is biologically inactive. It is the end stage of adenosine degradation in myocytes, but in the endothelial cells adenosine is broken down from inosine to hypoxanthine and uric acid. At physiological concentrations, adenosine is predominantly salvaged, i.e., metabolized to adenosine 5-monophosphate (AMP) by the enzyme adenosine kinase. At higher concentrations such as those following administration of diagnostic doses, adenosine is deaminated to inosine [4]. Dipyridamole blocks adenosine reuptake with a resultant increase of adenosine in extracellular space and greater activity on the receptor site. Theophylline and other methylxanthines (such as caffeine) block adenosine receptors in a dose-dependent manner [4] (Fig. 14.2). The main physiological effects of endogenous adenosine, classified according to involvement of A1, A2, or A3 receptors are presented in Table 14.2. When patients receiving adenosine (140 μg kg^{-1} per min) for controlled hypotension were pretreated with clinical doses of dipyridamole (to reduce the dose requirements of adenosine),

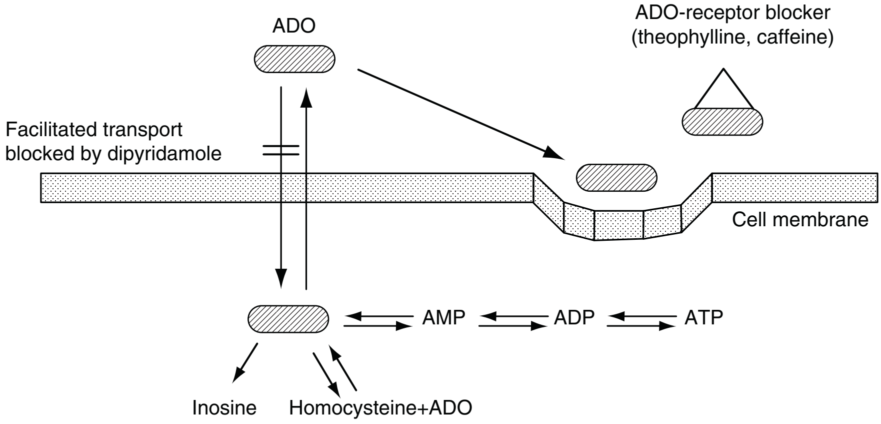

Fig. 14.2 Metabolism and mechanisms of action of adenosine in the coronary arteries. *ADO* adenosine, *AMP* adenosine monophosphate, *ADP* adenosine diphosphate, *ATP* adenosine triphosphate. (Modified from [4])

Table 14.2 Adenosine receptors: a view from the imaging laboratory

Receptor	Effect	Desired diagnostic end point
A1	Atrioventricular block Bradycardia Preconditioning	
A2A		Coronary vasodilation
A2B	Bronchoconstriction due to mast cell degranulation	
A3	Anti-inflammatory effects (peripheral blood mono-nuclear cells)	

Table 14.3 Cardiovascular effects of exogenous adenosine administered intravenously in humans

- Vagal inhibition (low doses), increase in heart rate
- Inhibition of the sinus node and AV conduction in high doses, bradycardia, AV block
- Antiadrenergic effect
- Vasodilatation in all arteriolar beds, except vasoconstriction in renal preglomerular arterioles; decrease in reperfusion injury
- Hyperventilation (explained by interaction with carotid chemoreceptors)

the arterial plasma concentration was 2.5 µM, a level ten times the normal level [19]. The adenosine effects listed in Table 14.3 substantiate the proposed potential clinical uses of adenosine listed in Table 14.4. Cardiac stress imaging is the most important diagnostic application of adenosine infusion. The intravenous infusion of adenosine induces a slight increase in heart rate and cardiac output, and a slight decrease in systemic pressure. The mild tachycardia occurs in spite of the direct, negative chronotropic and dromotropic effects of adenosine for stimulation of A1 myocardial receptors; it is a consequence of adrenergic activation, occurring either through direct stimulation of sympathetic excitatory arterial chemoreceptors [20] or indirectly, through systemic vasodilation. In normal subjects, the coronary blood flow increases to four to five times the baseline flow following adenosine – an increase comparable to that caused by high-dose dipyridamole and substantially higher than that induced by exercise or dobutamine, during which coronary blood flow increases about three times the baseline value [21]. The maximal coronary dilatory effect is reached within 2 min of adenosine administration and wears off rapidly within 2.5 min after the infusion is stopped. Adenosine can induce elevation in pulmonary capillary wedge pressure and/or left ventricular end-diastolic pressure only in presence of myocardial ischemia [22]. The power and time course of the coronary vasodilator effect of adenosine and other newer synthetic adenosine-receptor agonists are shown in Fig. 14.3 [14].

Table 14.4 Potential clinical uses of adenosine

• Paroxysmal supraventricular tachycardia
• Exercise-induced ventricular tachycardia
• Controlled hypotension during intracranial vascular surgeries
• Afterload reduction in congestive heart failure
• Antiplatelet aggregation (cardiopulmonary bypass, hemodialysis)
• Reduction of reperfusion injury
• Diagnosis and prognosis of coronary artery disease (13)

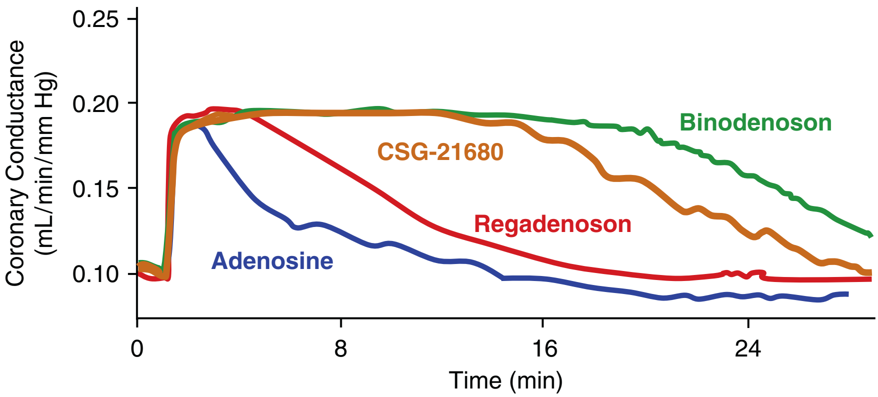

Fig. 14.3 The vasodilatory effect of adenosine and newer selective A2A receptor agonists. (Adapted from [33])

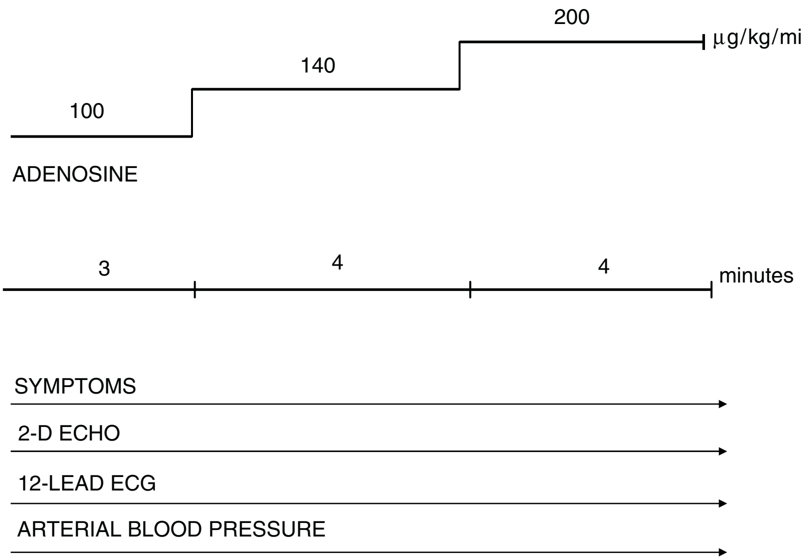

Fig. 14.4 Protocol of adenosine stress echocardiography

14.3 Methodology

For echocardiographic imaging, the dose is usually started at 100 µg kg^{-1} per minute and is increased gradually up to 200 µg kg^{-1} per minute [8] (Fig. 14.4). When side effects are intolerable, down-titration of the dose is also possible. Similar to dobutamine, administration of adenosine requires an infusion pump, whereas dipyridamole may be injected with a handheld syringe. As with dipyridamole, test sensitivity can be potentiated using a handgrip [23], which can be added to adenosine or to ATP infusion [24]. Some authors suggest infusing adenosine for no more than 90 s, taking into account that the maximal hyperemic effect is already reached at 30–60 s [25, 26]. The adenosine injection of 2.5 mg bolus produces an increment in coronary flow reserve similar to that obtained a by 3-min venous infusion and has no significant side effects [27]. The short adenosine infusion seems to be effective, safer, and better tolerated than the standard dosage, but it has the disadvantage that there is not enough time to assess contemporary left ventricular wall motion.

14.4 Tolerability and Safety

Side effects are very frequent and are limiting in a significant number of patients – up to 20% [28]. The most frequent limiting side effects include high-degree atrioventricular block, arterial hypotension, intolerable chest pain (sometimes unrelated to underlying ischemia,

Table 14.5 Side effects of pharmacological stress protocols

Stress protocol	Dipyridamole 0.56 mg kg^{-1}	Dipyridamole 0.84 mg kg^{-1}	Adenosine 140 mcg kg^{-1} per min	Dobutamine 40 mcg kg^{-1} per min ± atropine
Reference	Lette et al	Picano et al	Cerqueira et al	Picano et al
No. of patients	73,806 (9,066 with 0.75 or 0.84 mg kg^{-1})	10,451	9,256	2,949
Major side effects	0.04%	0.07%	<0.10%	0.4%
Fatal MI	0.01%	0.01%	0%	0%
Nonfatal MI	0.017%	0.02%	0.01%	0.07%
VT/VF	0.008%	0.01%	0%	0.05%

MI myocardial infarction, *VT* sustained ventricular tachycardia, *VF* ventricular fibrillation

possibly induced for direct stimulation of myocardial A1 adenosine receptors), shortness of breath, flushing, and headache. All side effects disappear upon termination of adenosine infusion. On very rare occasions, an infusion of aminophylline is required. The quality of side effects is similar to that experienced by the same patients during dipyridamole stress, but these effects are quantitatively more pronounced during adenosine stress. In one study [26], it was found that among adenosine, dipyridamole, and dobutamine, adenosine was the test most disliked by the patients. Although side effects are frequent, the incidence of major life-threatening complications (such as myocardial infarction, ventricular tachycardia, and shock) has been shown to be very low, with only one nonfatal myocardial infarction in approximately 10,000 cases. Among pharmacological stress tests [25–29], adenosine is probably the least well tolerated subjectively, but at the same time possibly the safest (see Table 14.5).

14.5 Diagnostic Accuracy for Detection of Coronary Artery Disease and Myocardial Viability

The full range of sensitivities has been reported [33–37, 7, 8, 26], with higher values coming from expert centers evaluating patients with previous myocardial infarction and multivessel disease (Table 14.6). Higher adenosine dose [8] and/or the combination with a handgrip [22] showed higher sensitivity without significant loss in specificity. On the basis of a recent meta-analysis on 11 studies, adenosine stress echocardiography, based on wall motion abnormalities, showed the same sensitivity (79%), specificity (91.5%), and accuracy as exercise echocardiography, dipyridamole echocardiography, and dobutamine echocardiography, with superior specificity when compared to SPECT stress imaging [38]. With last-generation (wall motion and coronary flow reserve, 11) three basic patterns can be identified during dual imaging adenosine stress echocardiography (Fig. 14.5): a normal response, with increased regional function and preserved coronary flow reserve (>2.0);

Table 14.6 Diagnostic accuracy of adenosine echocardiography

Authors	Reference	Year	Patients	Dose	Sensitivity (%)	Specificity (%)
Zoghbi et al.	33	1991	73	100–140	85	92
Edlund et al.	34	1991	54	60–200	89	Na
Martin et al.	35	1992	37	140	76	60
Marwick et al.	36	1993	97	180	86	71
Case et al.	37	1994	26	140	96	100
Takeishi et al.	38	1994	61	140	51	Na
Tawa et al.	39	1995	67	180	64	91
Djordievic al.	40	1996	58	200	92	88

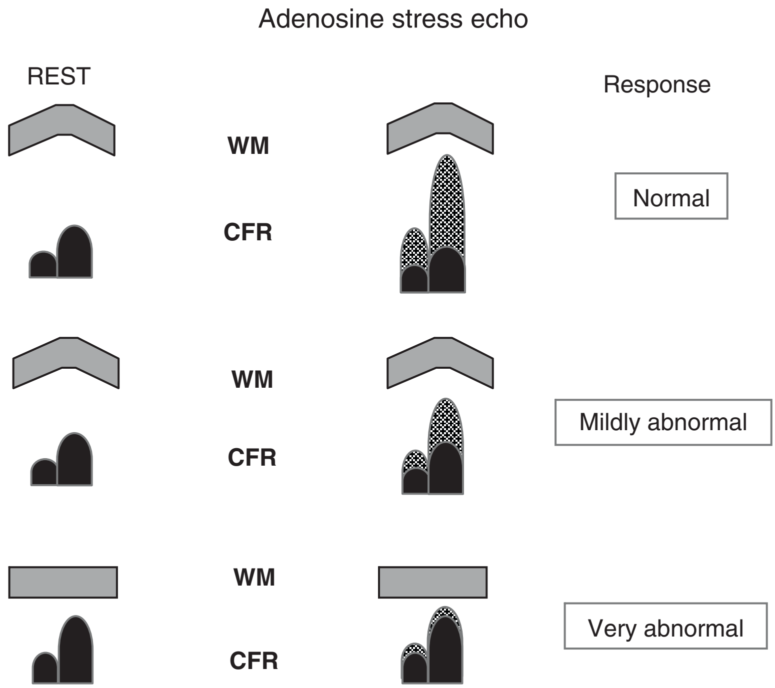

Fig. 14.5 Response patterns during dual imaging adenosine stress echocardiography: normal (hyperkinetic wall motion; greater than twofold increase in diastolic coronary flow velocity); mildly abnormal (normal wall motion but reduced hyperemic response); markedly abnormal (wall motion abnormalities that can be made even more malignant by concomitant reduction in coronary flow reserve in LAD territory)

an abnormal response, with reduction in coronary flow reserve (<2.0) but with normal wall motion response (indicative of microvascular disease or moderate epicardial coronary artery stenosis); and a markedly abnormal response with inducible wall motion abnormalities, suggestive of anatomically significant epicardial artery stenosis. Some initial data suggest that adenosine infusion may elicit an inotropic response in viable myocardium with resting dysfunction [39], thereby representing an alternative to dobutamine for the recognition of viability through pharmacological stimulation.

14.6 Prognostic Value

Data on the prognostic value of adenosine stress echocardiography findings are conspicuously lacking to date. By extrapolation from the wealth of data available with dipyridamole stress echocardiography [11, 40] and from more recent data with adenosine scintigraphy [40] and adenosine magnetic resonance imaging [41], it is reasonable to expect adenosine-induced wall motion abnormalities to identify troublemakers in the short run (within months), whereas isolate reduction in coronary flow reserve, without associated wall motion abnormalities, may identify troublemakers in the long run (years).

14.7 Indications and Contraindications

The merits and limitations of adenosine in comparison with the prototype vasodilator dipyridamole are shown in Table 14.7. The list of indications and contraindications to adenosine is identical to that for dipyridamole (Table 14.8). Exogenous adenosine has an even more pronounced negative chronotropic and dromotropic effect than endogenous adenosine [14], making the appearance of advanced atrioventricular blocks more frequent with adenosine than with dipyridamole for equivalent doses. Adenosine is a direct alternative to dipyridamole – the prototype of vasodilator adenosinergic stress. Like dipyridamole, antianginal drugs lower adenosine stress echocardiography sensitivity, whereas concomitant

Table 14.7 Adenosine versus dipyridamole for vasodilator stress testing

	Dipyridamole	Adenosine
Half-life	Hours	Seconds
Aminophylline requirement	Always	Almost never
Echocardiographic difficulty	Mild	Mild to moderate
Limiting side effects	5%	10–20%
Patient tolerance	Good	Beta-blockers
Prognostic value	Proven	Unknown

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Table 14.8 Patients with indications to adenosine stress echocardiography

	Indicated	Uncertain	Contraindicated
Indication to dual imaging vasodilatory stress echocardiography	√		
Unstable carotid disease	√		
Elderly patients	√		
Viability detection in patients intolerant to dobutamine		√	
Theophylline use, COPD, asthma			√
Previously intubated because of respiratory failure			√
History of first-degree (or greater) AV block or sinus mode disease without functioning artificial pacemaker			√
Intake of caffeine or other methylxanthine-containing foods (chocolate, tea, banana) for 24 h before stress			√

therapy with oral dipyridamole potentiates the cardiovascular effects of adenosine. The safety record and short half-life make adenosine especially indicated in patients with severe aortic stenosis [42] or elderly patients [43], who may be especially vulnerable to complications during dipyridamole or dobutamine stress. In some countries, an additional limitation of adenosine is its exorbitant cost: in the USA, adenosine costs $ 179, dipyridamole $ 95, and dobutamine $ 1 per exam. In Europe, adenosine costs € 100, dipyridamole € 3, and dobutamine € 9. However, it is also possible to have a galenic formulation of adenosine from the hospital pharmacy at a very low cost of around € 1. Possibly, more expensive third-generation selective A2A agonists may find a selective indication in patients with moderate and severe chronic obstructive pulmonary disease [44], who have an indication to stress imaging and may want to avoid adenosine-induced bronchoconstriction and respiratory compromise, although in these patients the use of the bronchodilator dobutamine might be more reasonable.

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