

Eliana Reyes

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## 2.1 Introduction

Cardiac stress testing, whether conducted alone [e.g., exercise electrocardiogram (ECG)] or combined with cardiac imaging, plays a major role in the diagnosis of coronary artery disease (CAD) by provoking myocardial ischemia and allowing the detection of myocardial perfusion abnormalities that arise from flow-limiting coronary stenosis. Most flow-limiting stenoses would otherwise go undetected, as compensatory dilation of the resistance vessels maintains resting myocardial blood flow within normal limits. During cardiac stress, hyperemic flow varies linearly with perfusion pressure, resulting in reduced myocardial perfusion as stenosis severity increases. This results in disparate distribution of myocardial blood flow and forms the basis for perfusion imaging. Depending on the severity of underlying stenosis and the magnitude of increase in oxygen demand, cardiac stress may induce myocardial ischemia, which would result in angina, ECG and hemodynamic changes, and myocardial contractile dysfunction in addition to perfusion abnormalities. Cardiac

stress imaging therefore provides valuable diagnostic information to guide clinical decision making with regard to medical therapy and revascularization. Dynamic exercise and pharmacological stress agents are used for this purpose, with newly developed agents able to overcome some of the limitations of existing methods. How to stress the human heart is a question that can only be answered after a comprehensive understanding of the properties and mechanism of action of the various forms of stress currently available. This chapter is dedicated to the several modalities of cardiac stress used to assess patients with known or suspected CAD undergoing noninvasive cardiac imaging.

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## 2.2 Dynamic Exercise

Isotonic or dynamic exercise is the most physiological form of cardiac stress and induces coronary hyperemia by increasing heart work and metabolic demand, hence provoking secondary coronary vasodilation. Maximal exercise can provoke a two to threefold increase in myocardial blood flow within a normal vascular territory. An optimal exercise test can add important diagnostic and prognostic information to imaging results by unveiling ischemic ECG and hemodynamic changes and allowing study of the relationship between symptoms and workload and assessment of exercise capacity, a well-recognized and independent predictor of adverse cardiac events.

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E. Reyes (✉)  
Nuclear Medicine Department,  
Royal Brompton Hospital, London, UK  
e-mail: e.reyes@rbht.nhs.uk

**Table 2.1** Contraindications to exercise testing

Absolute
• Recent acute or complicated myocardial infarction or unstable angina
• Known significant left-main-stem stenosis
• Acute or decompensated heart failure
• Untreated life-threatening arrhythmias
• Severe dynamic (e.g., HOCM) or fixed (e.g., aortic valve stenosis) LVOTO
• Poorly controlled and severe systemic hypertension
• Recent pulmonary embolism or infarction
• Severe pulmonary hypertension
• Acute systemic or cardiac inflammatory process or acute illness
Relative
• Reduced exercise capacity (e.g., orthopedic, musculoskeletal, or neurological condition that precludes dynamic exercise)
• Poor motivation or willingness to exercise

*HOCM* hypertrophic obstructive cardiomyopathy; *LVOTO* left ventricular outflow tract obstruction

## 2.2.1 Indications

Exercise is indicated in patients physically able and sufficiently motivated to reach an adequate level of cardiac work that would ensure a maximal or near-maximal coronary hyperemic response (Table 2.1). Preparation is similar to that of conventional exercise ECG with the exception that patients should be advised to refrain from methylxanthine-containing products, as vasodilator stress may be undertaken if the patient fails to complete the exercise test (see Sect. 2.3). Anti-ischemic drugs, especially beta-adrenergic blockers, may lead to a rise in ischemic threshold, which may reduce the sensitivity of diagnostic imaging [1]. Anti-ischemic drugs should therefore be discontinued for a minimum of five half-lives before the exercise test.

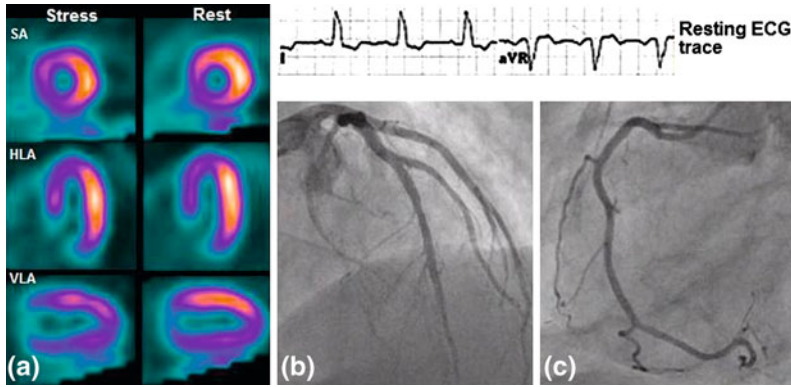
## 2.2.2 Contraindications

In addition to the well-known contraindications to exercise testing (Table 2.1), exercise should be avoided in patients with left bundle branch block (LBBB) and paced ventricular rhythm. This is particularly relevant to myocardial perfusion scintigraphy (MPS), as exercise is

associated with a high incidence of septal defects on stress images in the absence of obstructive CAD (Fig. 2.1). The exact underlying mechanism remains unknown. Although it has been attributed to a true reduction in perfusion to the septum, recent evidence suggests that the temporal delay between left and right ventricular activation in LBBB may result in reduced septal thickening and decreased counts in the septum due to partial volume effect [2]. The rise in heart rate that occurs during exercise would increase the probability of septal defects arising from the conduction abnormality.

## 2.2.3 Protocols

Currently available protocols involve continuous exercise with incremental workloads between multiple stages, producing a progressive increase in myocardial oxygen demand. The choice of one protocol over the others depends on the patient's physical conditioning and familiarity with exercise (e.g., walking versus cycling). The treadmill Bruce protocol is the most commonly indicated test because it involves large increments in workload, allowing most patients to reach their maximal or near-maximal exercise capacity over a relatively



**Fig. 2.1** Stress/rest myocardial perfusion scintigraphy (a) shows an extensive and partially reversible perfusion abnormality involving the septum and adjacent antero-septal and inferoseptal regions in a patient with *LBBB* left

bundle branch block on his resting *ECG* electrocardiogram, and normal left and right coronary arteries on subsequent coronary angiogram. (b, c) SA short axis, HLA horizontal long axis, VLA vertical long axis

short period. Regardless of the protocol used, an optimal exercise test should be symptom limited, with the patient achieving at least 85% of their age—and gender-adjusted maximum predicted heart rate unless cardiac symptoms and ischemic ECG changes develop (i.e.,  $>1$  mm ST-segment elevation in non-Q-wave leads or  $\geq 2$  mm horizontal or downsloping ST-segment depression at 60–80 ms after the J point in three or more consecutive beats on any ECG lead). At this point, the perfusion tracer is administered intravenously followed by a saline flush. After this, it is recommended that the patient continue exercising for at least 2 min to allow for adequate myocardial extraction of tracer (MPS protocol).

#### 2.2.4 Diagnostic Performance and Accuracy

There is variation in the reported accuracy of exercise testing when combined with diagnostic imaging, partly because of differences in protocols and standards of interpretation. For instance, the sensitivity of exercise MPS for detecting coronary stenosis is in the region of 85%, whereas its specificity for ruling out disease is about 75% [3]. It is important to emphasize that the adequacy of the exercise test influences the diagnostic performance of cardiac

imaging, as failure to increase myocardial oxygen demand may prevent detection of abnormal coronary vasodilator reserve. Hence, pharmacological stress must be considered in patients who fail to reach an exercise endpoint and in those expected to perform suboptimally.

#### 2.2.5 Safety

Serious adverse events during exercise are uncommon, but the incidence increases in high-risk populations, such as those with severe multivessel CAD and impaired left ventricular function. In general, there is a 1 in 10,000 risk of cardiac death or fatal myocardial infarction (MI) and a 1 in 5,000 risk of nonfatal MI or life-threatening complications during exercise testing [4].

### 2.3 Pharmacological Agents

#### 2.3.1 Vasodilators

These agents cause primary or direct coronary vasodilation independent of heart work and comprise two categories: (1) adenosine receptor agonists, which can be classified further

according to their selectivity for the adenosine receptor (nonselective agonists, adenosine; selective agonists, regadenoson, apadenoson, and binodenoson); (2) inhibitors of adenosine metabolism and breakdown (dipyridamole). In general, vasodilators cause a greater increase in blood flow, up to four to five times its resting level, than dynamic exercise. Importantly, these potent vasodilators may abolish coronary autoregulation; in the presence of significant epicardial stenosis, their administration may induce myocardial ischemia, especially in the subendocardium (see Sect. 3.1.1). Vasodilator stress has several practical advantages over exercise, including flexibility (as physical limitations would not affect test performance), high reproducibility, and the need for little or minimal motivation and cooperation from the patient. There are also a few disadvantages, such as inability to monitor adequacy of stress and the fact that it is not possible to assess the relationship between physical activity, metabolic stress, and symptoms.

### 2.3.1.1 Adenosine

Adenosine is a naturally occurring purine nucleoside composed of a molecule of adenine and ribose joined by a  $\beta$ -N<sub>9</sub>-glycosidic bond. Over recent decades, it has become increasingly clear that adenosine plays a major role in the adaptation to inadequate oxygen supply by regulating several biological functions by activating adenosine receptors A<sub>1</sub>, A<sub>2A</sub>, A<sub>2B</sub>, and A<sub>3</sub>. In the cardiovascular system, adenosine reduces workload to the heart, slowing the heart rate by inhibiting sinus atrial (SA) node activity and delaying atrioventricular (AV) node conduction [5]. It also attenuates myocardial contractility that results from beta-adrenergic stimulation. However, the earliest response to a myocardial oxygen supply–demand imbalance is a rise in interstitial adenosine and a reduction in coronary vascular resistance [6]. Adenosine dilates the small resistance vessels by binding to adenosine A<sub>2A</sub> receptors located on the surface of arteriolar smooth muscle cells [5]. Activation of this receptor subtype increases cellular cyclic

adenosine monophosphate (cAMP), which in turn mediates the opening of potassium adenosine triphosphate (K<sub>ATP</sub>) channels and decreases calcium (Ca<sup>2+</sup>) uptake, causing smooth muscle relaxation [7]. Adenosine can also dilate the large conductance vessels by an endothelium-dependent flow-mediated mechanism, but this effect is rather modest and does not relate to the severity of coronary stenosis [8].

Adenosine has a rapid onset of action, with average time from infusion initiation to maximal coronary vasodilator response being achieved in little more than 80 s [9]. It is rapidly taken up by erythrocytes and endothelial cells following its intravenous administration, which explains the very short half-life (<10 s) and thus the need for continuous administration [10].

At the recommended dose for perfusion imaging (i.e., 140 mcg/kg/min), adenosine provokes maximal coronary vasodilation with a peak blood-flow velocity similar to that observed after intracoronary papaverine [9]. This leads to a fourfold increase in myocardial perfusion, with absolute values in the region of 4.5 mL/min/g [11, 12]. No further increase in coronary blood flow occurs at higher infusion rates. Smaller doses of adenosine can provoke maximal hyperemia but are associated with wide fluctuations in coronary vascular resistance [9]. In the presence of flow-limiting coronary stenosis, myocardial perfusion abnormality is primarily the result of heterogeneous distribution of blood flow. However, adenosine may induce myocardial ischemia through coronary steal. This phenomenon is characterized by a fall in driving pressure for collateral flow from normal to stenotic coronary territories as a result of the greater vasodilator response of the normal vascular bed to adenosine (intercoronary steal) [13]. Intercoronary steal is rare but relatively more prevalent among elderly patients with severe multivessel CAD. Blood-flow diversion from subendocardium to subepicardium may also occur (intracoronary steal) [14].

The peripheral hemodynamic response to 140  $\mu$ g/kg/min of adenosine is rather modest, with an average decrease in both systolic and diastolic blood pressure of approximately

**Table 2.2** Side effects during adenosine stress

Side effect	Adenosine only <i>n</i> = 9,256 <sup>a</sup> (%)	Adenosine and exercise <i>n</i> = 1,261 <sup>b</sup> (%)
Any symptom	81	56
Chest pain	35	17
Dyspnea	35	30
Flushing	37	7
Headache	14	5
Nausea	15	2
Dizziness	10	1

<sup>a</sup> Frequency  $\geq 5\%$ . Modified from [15]

<sup>b</sup> Reyes et al. [57]

10 mmHg and a heart rate increase in the region of 10 bpm, and this is an important advantage over other equally potent coronary vasodilators that can have a profound effect on peripheral resistance and blood pressure [9, 15]. Importantly, the systemic response to adenosine bears no predictable relationship to its coronary effect, and hence positive image findings may be seen in patients with a blunted hemodynamic response to adenosine [16]. This phenomenon has been attributed to differing receptor-affinity thresholds, variations in tissue-receptor reserve, cardiac output, and adrenergic and vagal tone, which might influence delivery and response to adenosine by the heart and other tissues and organs [17, 18].

Activation of receptors other than the coronary A<sub>2A</sub> subtype occurs at vasodilator doses of adenosine. This nonselective activation is responsible for most adenosine-related side effects (Table 2.2). Although side effects are fairly common, they are usually mild and well-tolerated, although occasionally more significant [15].

### 2.3.1.2 Regadenoson

Regadenoson is among the newly developed selective adenosine A<sub>2A</sub> receptor agonists and the only one commercially available. Regadenoson is a 2-[N-1-(4-N-methylcarboxamidopyrazolyl)]-adenosine derivative. Early receptor binding and tissue response experiments, as well as ex vivo isolated heart models, show a high

binding and functional selectivity of regadenoson for the adenosine A<sub>2A</sub> receptor, with minimal or no activity or binding for other adenosine receptors [19, 20]. These studies also show that regadenoson is more potent than adenosine at inducing coronary arteriolar vasodilation, with a half maximal effective concentration (EC<sub>50</sub>) of 6.4 nM versus 59 nM for adenosine [19, 20].

The effect of regadenoson on the coronary circulation is concentration dependent, with single doses of 100, 300, 400, and 500 mcg causing a threefold increase in peak coronary blood-flow velocity [21]. Unlike lower doses, 400 and 500 mcg doses showed a sustained effect that lasted for at least 2 min, providing sufficient time for adequate myocardial extraction of tracer. Fewer side effects were reported with the 400 mcg dose. Subsequent studies demonstrate that body weight and body mass index (BMI) have no effect on the volume of distribution or total body clearance of regadenoson and do not appear to alter its efficacy for detecting inducible myocardial perfusion abnormality [22–24]. This evidence supports the use of a single dose of 400 mcg, which is characterized by a rapid onset of action, with peak coronary vasodilation by 30 s following intravenous administration and a short-lasting effect (<5 min). Importantly, there is no need for dose adjustment in patients with renal or hepatic failure [25, 26].

There is a modest decrease in both systolic and diastolic blood pressure of approximately 10 mmHg and an average increase in heart rate

of 25 bpm following an intravenous injection of 400 mcg [27]. The magnitude of increase in heart rate is out of proportion to the decrease in blood pressure, and this has been attributed to direct stimulation of adenosine A<sub>2A</sub> receptors on the sympathetic nerve endings [28].

Clinical trials show that regadenoson has a side-effect profile similar to that of adenosine, although there are some variations between agents with regard to type, quality, and duration of side effects [27]. In general, most side effects are short lived, mild, and well tolerated. When compared with adenosine, test tolerability is better after regadenoson [22, 23].

### 2.3.1.3 Dipyridamole

Dipyridamole was the first vasodilator agent used for diagnostic imaging. It has a lipophilic pyrimidine base that inhibits cellular reuptake of endogenous adenosine and its breakdown, hence increasing its interstitial concentration [29]. The maximal coronary vasodilator response to dipyridamole is similar to that of exogenous adenosine, but adenosine is often preferred over dipyridamole because of its rapid onset of action and shorter half-life (10 s versus 30 min for dipyridamole) [30]. Dipyridamole causes fewer side effects than adenosine but they tend to last longer; administration of an adenosine receptor antagonist such as aminophylline is often required [31]. Despite this, the safety profile of dipyridamole is comparable with that of adenosine, but prolonged action and side effects can be seen in patients with liver failure owing to its hepatic metabolism [31].

## 2.3.2 Indications

Vasodilator stress is commonly indicated in patients with a contraindication to exercise or when it is not possible to obtain an adequate exercise test (Table 2.1). Vasodilators should be considered the first-line test in patients with LBBB or paced rhythm on their resting ECG because of the lower incidence of tachycardia-related artefacts on diagnostic imaging.

Preparation for vasodilator stress includes abstention from methylxanthine-containing products, including coffee, tea, chocolate, caffeinated drinks and food, aminophylline, and theophylline for a minimum of 24 h prior to the test. Methylxanthines are competitive antagonists to the adenosine receptors and at concentrations commonly encountered in daily life may prevent the action of adenosine agonists (Fig. 2.2). Dipyridamole should be withheld for 48 h because it blocks adenosine transport and may prolong its effects. Discontinuation of antianginal drugs before vasodilator stress remains controversial, with limited evidence suggesting that beta-blockade may attenuate blood-flow heterogeneity induced by primary vasodilators (Fig. 2.3) [32–34].

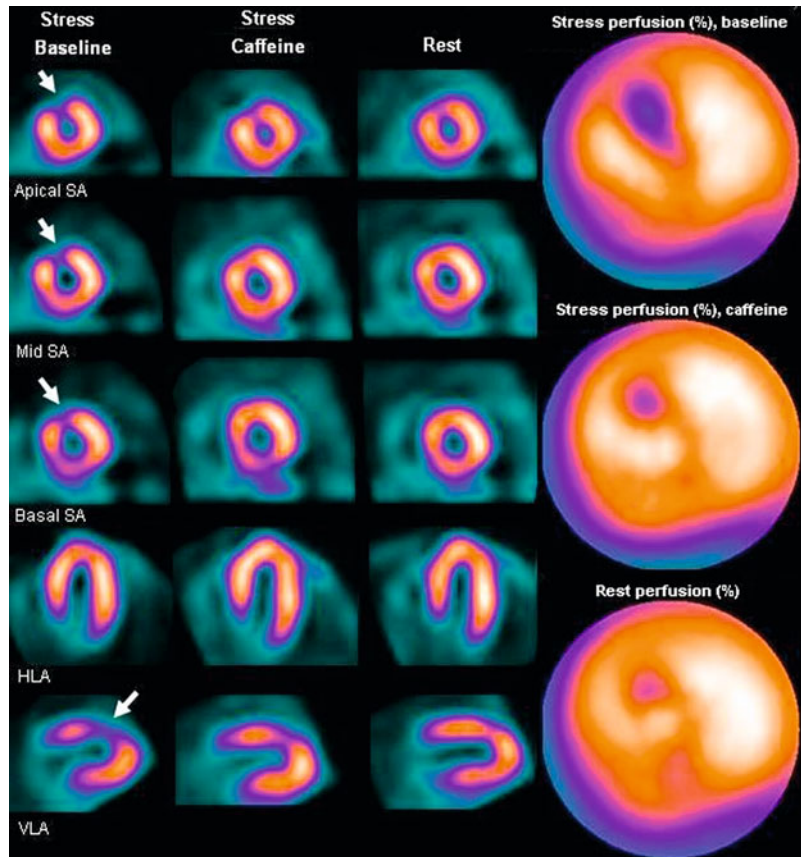
## 2.3.3 Contraindications

In general, vasodilator stress should be avoided in patients with a history of severe obstructive airways disease or ongoing bronchospasm, advanced degree of atrioventricular block without a functioning pacemaker, symptomatic hypotension, and recent methylxanthine or dipyridamole use [35, 36].

Bronchospasm represents the commonest noncardiac adverse event caused by vasodilators and occurs almost exclusively in patients with obstructive airway disease. Adenosine and dipyridamole are therefore contraindicated in patients at high risk for or with ongoing bronchospasm. Regadenoson is not contraindicated in obstructive airway disease but should be administered with caution in these patients. Vasodilators should be avoided in patients with hypotension (i.e., blood pressure <90/60 mmHg) because of the potential for exacerbation owing to a reduction in vascular resistance, and in advanced degrees of AV block without a functioning pacemaker or with sick sinus syndrome because of the increased risk of rhythm disturbances. Further evidence is needed regarding safety and tolerability of regadenoson in patients with severe forms of obstructive airways disease and in patients with advanced



**Fig. 2.2** Caffeine (serum caffeine level = 4.1 mg/L) attenuates the extent and depth of inducible perfusion abnormality (arrows) after 140 mcg/kg/min of adenosine in a patient with previous CABG (coronary artery bypass graft) [*LIMA*, left internal mammary artery to *LAD*, left anterior descending artery, vein grafts to *LCx*, left circumflex artery, and *RCA*, right coronary artery] and recurrent symptoms. SA short axis, HLA horizontal long axis, VLA vertical long axis



degrees of AV block. Although recent caffeine consumption is a contraindication to regadenoson stress, a study in healthy volunteers suggests that at the recommended dose of 400 mcg, regadenoson may overcome the antagonism mediated by caffeine on the adenosine receptors [37]. Further evidence is forthcoming in patients undergoing regadenoson MPS before and after caffeine intake [38].

### 2.3.4 Protocols

#### 2.3.4.1 Adenosine

Standard protocol consists of an intravenous infusion of 140 mcg/kg/min of adenosine for 6 min, with tracer injection after 3 min of infusion (Fig. 2.4). Because of its rapid onset of action, several studies investigated the

effectiveness of shorter adenosine protocols, observing a similar accuracy for detecting coronary stenosis with a 4- and 5- versus 6-min infusion [39]. Shorter infusion times (<4 min) were associated with smaller perfusion abnormalities on stress images; this may compromise diagnostic performance and should therefore be avoided [40, 41]. Coronary blood flow would return to baseline 1–2 min after termination of adenosine infusion. Adenosine may be coupled with dynamic or isometric exercise to reduce the incidence and severity of untoward effects (Table 2.2). Exercise is particularly effective in reducing the incidence of cardiac conduction abnormalities and intensity and frequency of side effects that result from the peripheral vasodilator effect of adenosine (e.g., headache, flushing, hypotension), hence improving test tolerability [42]. When combined with MPS, supplemental exercise is associated with better

**Fig. 2.3** Tomograms (upper panel) and polar maps (lower panel) show a mild but extensive adenosine-induced perfusion abnormality in the lateral wall (arrows) that is no longer present after beta-blockade. SA short axis, HLA horizontal long axis

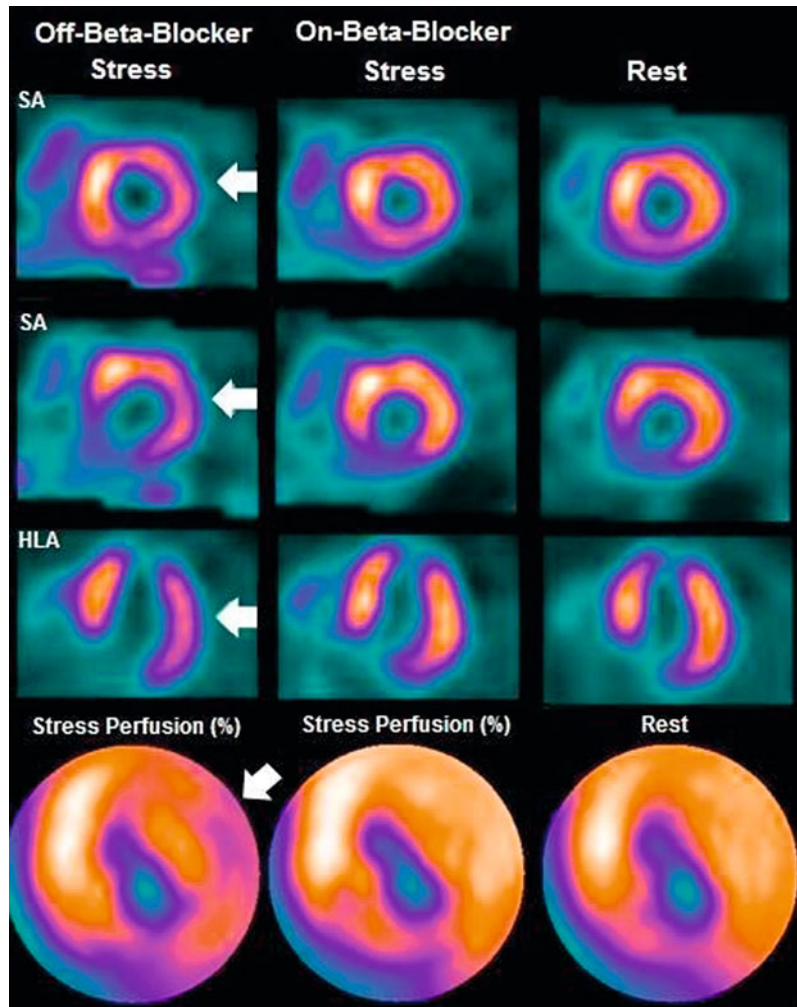


image quality. Exercise enhances image quality by provoking splanchnic vasoconstriction, which reduces the extracardiac accumulation of tracer, thus increasing heart-to-background tracer-activity ratio [43]. Exercise may also enhance the detection of inducible myocardial perfusion abnormality, and this seems to be independent of its effect on image quality. Nearly 60% of all vasodilator stress tests are combined with exercise [44].

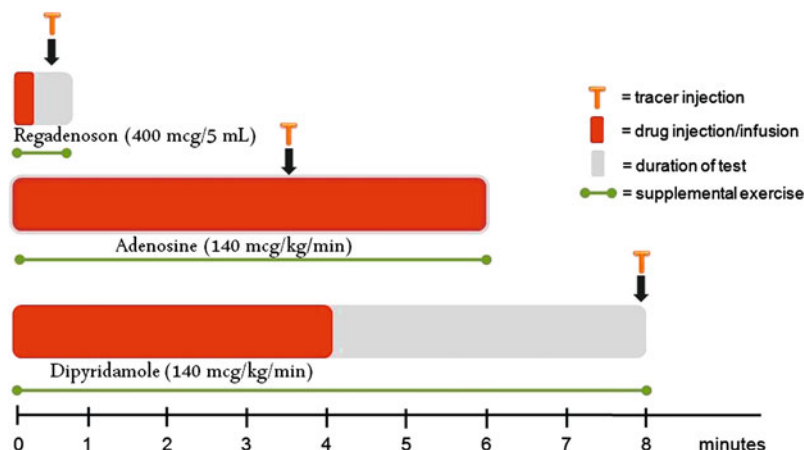
In patients with well-controlled or mild asthma or chronic obstructive pulmonary disease (COPD), adenosine can be given as a titrated protocol starting at a low dose of 70–100 mcg/kg/min for 1 min and increasing if tolerated up to 140 mcg/kg/min, with tracer injection 2 min

after the maximal dose of 140 mcg/kg/min [45, 46]. A beta-2 adrenergic agonist inhaler, such as salbutamol, can be given prior to starting the adenosine infusion. In patients reporting recent caffeine consumption (<12 h) there is evidence that a 50% increase in adenosine dose (210 mcg/kg/min) may overcome the attenuating effect of caffeine contained in beverages such as coffee and tea [47].

#### 2.3.4.2 Regadenoson

Regadenoson is administered intravenously as a single dose of 400 mcg over 10 s, followed immediately by a 10-mL saline flush with tracer injection 10–20 s after saline injection. No dose





**Fig. 2.4** Protocols for vasodilator stress myocardial perfusion imaging according to pharmacological agent. Heart rate, blood pressure, and *ECG* electrocardiogram

adjustment for patient weight or renal or hepatic function is required. Regadenoson is well tolerated, and most side effects are mild and short lived, but some symptoms may last up to 30 min. Aminophylline may be used to counteract persistent or intolerable symptoms. As with the other vasodilators, the addition of exercise may help reduce the incidence and severity of side effects and improve test tolerability [48].

### 2.3.4.3 Dipyridamole

Dipyridamole is given intravenously at 140 mcg/kg/min for 4 min (Fig. 2.4). As with the other vasodilators, it can be combined with exercise to minimize side effects and improve image quality when performed with MPS. Coronary hyperemia reaches a peak 3–4 min after completion of the infusion, at which point the tracer should be injected. As would be expected, hyperemic response to dipyridamole is equivalent in magnitude to that provoked by adenosine [30].

## 2.3.5 Diagnostic Performance and Accuracy

High accuracy for CAD detection is documented for vasodilator stress when combined with

should be monitored throughout. All vasodilators can be coupled with submaximal isotonic (dynamic) or isometric exercise

diagnostic imaging. The sensitivity of adenosine MPS for detecting angiographically significant epicardial coronary stenosis ( $\geq 70\%$  luminal diameter reduction) is in the region of 90%, with a specificity ranging from 75 to 100% [3]. Diagnostic accuracy of dipyridamole MPS is similar to that of adenosine [3]. With regard to regadenoson, data from two large randomized clinical trials demonstrate that regadenoson MPS is not inferior to adenosine MPS for detecting inducible perfusion abnormality [27]. Indeed, good agreement between regadenoson and adenosine MPS has been found for several imaging variables [22, 27]. Furthermore, quantitative assessment of myocardial perfusion using a normal database suggests that the scintigraphic information obtained after regadenoson administration is almost identical to that following adenosine stress [49].

## 2.3.6 Safety

Adenosine stress has an excellent safety profile, with an estimated risk for death or nonfatal MI of less than 1 in 10,000 cases [15]. A similar low event rate is documented when adenosine is administered as early as 48–72 h after an uncomplicated acute coronary syndrome [50]. The safety profile of dipyridamole is similar to

that of adenosine, and pooled data so far suggest that regadenoson is equally as safe [31, 51]. Vasodilator stress should be stopped if symptomatic hypotension, bronchospasm, persistent and/or symptomatic arrhythmia, or signs and symptoms suggestive of severe myocardial ischemia occur.

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## 2.4 Inotropic Agents

### 2.4.1 Dobutamine

Dobutamine is the only inotropic drug used for pharmacological stress testing. The value of dobutamine stress for perfusion imaging has not been documented as extensively as for the primary vasodilators, and estimates of its diagnostic accuracy vary significantly across publications. The latter is attributed to inadequate protocols, lack of standardized endpoints, and concomitant use of beta-adrenergic receptor blockers. In addition, the hyperemic effect of dobutamine is less predictable than that of primary vasodilators, and individual responses are highly variable and, in some cases, suboptimal. As a result, dobutamine is recommended only in patients in whom other forms of stress are not possible or are contraindicated.

Dobutamine is a sympathomimetic agent and a synthetic analog of dopamine. It exerts a potent  $\beta_1$ -adrenergic receptor-agonist action and a less profound  $\beta_2$ - and  $\alpha_1$ -adrenergic receptor-agonist effect. At low doses ( $<20$  mcg/kg/min), dobutamine exerts a predominant inotropic effect, increasing myocardial oxygen demand and provoking secondary coronary vasodilation and hyperemia. At higher doses, further activation of  $\beta_1$ -adrenoceptors results in a predominant chronotropic effect. The net effect is an increase in heart rate, myocardial contractility, cardiac output, and a small increase in blood pressure [52]. In some patients, vigorous myocardial contraction may activate intramyocardial mechanoreceptors, which cause sympathetic withdrawal and enhance parasympathetic activity. This is known as the vasodepressor Bezold–Jarisch reflex. As a result, paradoxical sinus

deceleration and marked hypotension develop. This paradoxical response has also been associated with angiographically significant coronary stenosis and significant underlying ischemia [53].

The onset of action of dobutamine occurs 2 min after intravenous infusion initiation and reaches a peak 5–10 min later. The increase in myocardial perfusion is dose dependent; at doses  $\geq 20$  mcg/kg/min, dobutamine increases myocardial perfusion two to three times its resting value [54]. Dobutamine has a half-life of approximately 2 min owing to its rapid hepatic metabolism.

### 2.4.2 Indications

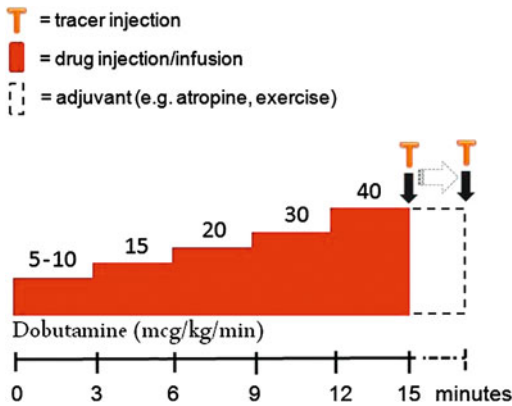
Contrary to its primary role in assessing myocardial contractile function and detecting ischemia-induced wall-motion abnormality, dobutamine is regarded as a third-line agent for perfusion imaging. It is mainly indicated when exercise is not possible and vasodilator stress is contraindicated. Preparation for dobutamine stress includes discontinuation of beta-adrenergic receptor antagonists for a minimum of five half-lives.

### 2.4.3 Contraindications

Because of its sympathomimetic effect, contraindication to dobutamine stress is similar to that of dynamic exercise, including recent acute coronary syndrome, untreated severe arrhythmias, and severe or uncontrolled hypertension. Dobutamine should also be avoided in patients with severe dynamic or fixed left ventricular outflow-tract obstruction. As for exercise, dobutamine is not ideal in patients with LBBB and ventricular paced rhythm, as these may cause artefactual perfusion abnormalities of the septum on stress MPS.

### 2.4.4 Protocol

Dobutamine is infused intravenously starting at 5 or 10 mcg/kg/min and increasing to 15, 20, 30,



**Fig. 2.5** Protocol for dobutamine myocardial perfusion scintigraphy (MPS). Protocol varies from center to center, but it normally consists of a stepwise IV injection of dobutamine starting at 5–10 mcg/kg/min and increasing by 5 or 10 mcg/kg/min every 3 or 5 min up to the maximal dose of 40 mcg/kg/min. The tracer is injected after 3–5 min on the maximal dose. In some centers, an adjuvant such as atropine is administered if  $\geq 85\%$  of maximal predicted heart rate is not achieved at the maximal dose. Heart rate, blood pressure, and electrocardiogram (ECG) should be monitored throughout the test

and 40 mcg/kg/min at 3–5 min intervals (Fig. 2.5). The tracer is injected after 3–5 min on the maximal dose of 40  $\mu\text{g/kg/min}$  unless myocardial ischemia develops or age—and gender-adjusted maximal predicted heart rate is reached. In patients unable to reach maximal or near-maximal predicted heart rate, 0.25–2.0 mg of atropine, a competitive antagonist of muscarinic cholinergic receptors, can be administered intravenously. Atropine increases heart rate through blockade of vagal effects on  $M_2$  receptors in the sinoatrial (SA) node. Side effects are rare, but atropine intoxication at relatively low doses ( $<1$  mg) have been documented in the elderly.

Dobutamine can also be coupled with supplemental low-level exercise to prevent hypotension and improve test tolerability. Exercise may enhance image quality by reducing background liver and gut activity and may provide additional chronotropic and inotropic stimulation, with a further increase in myocardial oxygen demand [55].

## 2.4.5 Diagnostic Performance and Accuracy

Stress imaging with dobutamine has a diagnostic accuracy similar to that of exercise and vasodilators. The reported sensitivity of dobutamine MPS for detecting coronary stenosis is in the region of 80–90%, with a specificity ranging between 64 and 100% [52]. Sensitivity increases when atropine is added (from 82 to 90%) without compromising specificity [52].

## 2.4.6 Safety

The commonest side effects during dobutamine infusion are symptomatic hypotension, tachyarrhythmias, chest pain, and dyspnea, which usually respond to appropriate medical care. The safety profile of dobutamine is similar to that of other modalities of stress, but complications may arise in high-risk populations. In nuclear cardiology practice, the reported incidence of sustained ventricular tachyarrhythmias, nonfatal myocardial infarction, and cardiac death during dobutamine stress is low [52, 56].

## 2.5 Conclusion

Cardiac stress is an essential part of diagnostic imaging, and current practice relies on a number of methods that are effective at characterizing the hemodynamic significance of coronary obstruction and its impact on myocardial perfusion. A large body of evidence supported by expert consensus and anecdotal experience indicate that all existing methods are safe when performed appropriately, and their diagnostic accuracies are comparable. It is important to bear in mind that inadequate patient preparation and inappropriate use of any of these forms of stress may lead to a significant reduction in diagnostic accuracy of stress imaging. Moreover, it is advised that each imaging center regularly monitors local competence, diagnostic

accuracy, and safety according to the different modalities of stress used.

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