Pathogenetic Mechanisms of Stress

5

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For a rational use of stress tests and an appropriate interpretation of their results, it may be useful to adopt a pathogenetic classification, taking into account the diagnostic end point of the test. Tests inducing vasospasm (ergonovine infusion and hyperventilation) explore the functional component. Tests trying to unmask coronary stenosis (exercise, dipyridamole, adenosine, dobutamine, pacing) mostly explore the ceiling of coronary reserve as defined by organic factors (Fig. 5.1). Some of these stressors (such as exercise) may also induce variations in coronary tone which can be superimposed on the organic factors, thus blurring the correlation between coronary anatomy and test positivity.

5.1 Ischemia and Vasospasm

Since coronary vasospasm can coexist with any degree of coronary stenosis, the presence of angiographically normal coronary arteries does not rule out the possibility of vasospastic myocardial ischemia; on the other hand, a "significant" coronary stenosis at angiography does not automatically establish a cause–effect relationship between organic disease and myocardial ischemia. In the past 20 years, we have come to appreciate the fact that the endothelium serves not only as a nonthrombogenic diffusion barrier to the migration of substances into and out of the blood stream, but also as the largest and most active paracrine organ in the body, producing potent vasoactive, anticoagulant, procoagulant, and fibrinolytic substances. Normal endothelium produces two vasoactive and platelet-active products, prostacyclin and EDRF, which act in concert to inhibit platelet adhesion and aggregation and relax vascular smooth muscle [1]. Normal endothelium also opposes a variety of vasoconstrictive stimuli, including catecholamines, acetylcholine, and serotonin, and it enhances the vasorelaxant effects of dilators, such as adenosine nucleotides. In the presence of a dysfunctional endothelium, vasodilatory stimuli – such as adenosine or dipyridamole – may become less potent, and vasoconstrictive stimuli much more effective [1] (Fig. 5.2). The mechanisms of coronary spasm are still unclear. No specific receptor subtypes appear to be involved, since a variety of physical and pharmacological stimuli

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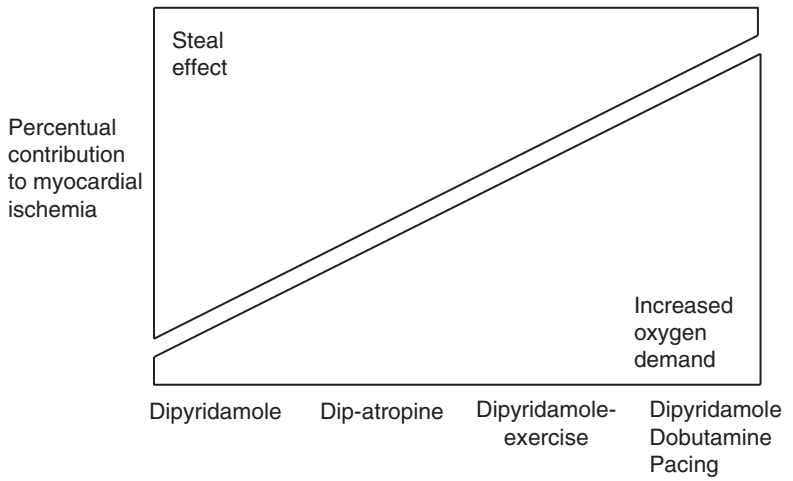

Fig. 5.1 Conceptual allocation of the tests employed in combination with echocardiography to induce ischemia via coronary vasospasm (*left*), coronary stenosis (*right*), or both mechanisms

can provoke spasm and no specific antagonist has proved capable of preventing it. The smooth muscle cell in the medial layer of coronary epicardial arteries reacts to several vasoconstrictive stimuli, coming centripetally from the adventitial layer (such as α-mediated vasoconstriction), or centrifugally from the intima–blood interface (such as endothelin and serotonin). In fact, serotonin has a vasodilatory effect on normal human myocardial arteries, which is mediated by endothelium-derived relaxing factors; when the endothelium is damaged, as in coronary artery disease, serotonin has a direct, unopposed vasoconstrictive effect [1]. Clinically, coronary vasospasm can be elicited by ergonovine maleate, an ergot alkaloid which stimulates both β-adrenergic and serotonergic receptors, and therefore exerts a direct constrictive effect on vascular smooth muscle. Hyperventilation induces spasm through systemic alkalosis. Physiologically, a powerful calcium-antagonistic action is exerted by hydrogen ions, which appear to compete with calcium ions for the same active sites both in the transmembrane calcium transport system and in the myofibrillar ATPase. Thus, vasoconstriction occurs if either calcium ion concentration increases or hydrogen ion concentration decreases. Exercise can also induce an increase in coronary tone, up to complete vasospasm, through α-sympathetic stimulation [2]. Dobutamine has a vasospastic and coronary vasoconstrictive effect mediated by α-adrenergic stimulation [3, 4]. Dipyridamole has no coronary constrictive effects per se; however, interruption of the test by aminophylline (which blocks adenosine receptors but also stimulates α-adrenoreceptors) can evoke coronary vasospasm in one-third of patients with variant angina [5]. Tests exploring organic coronary stenosis can induce ischemia by means of two basic mechanisms: (a) an increase in oxygen demand, exceeding the fixed supply and (b) flow maldistribution due to inappropriate coronary arteriolar vasodilation triggered by a metabolic/pharmacological stimulus. The main pharmacodynamic actions of dobutamine and dipyridamole stresses are summarized in Tables 5.1 and 5.2, respectively. Dobutamine

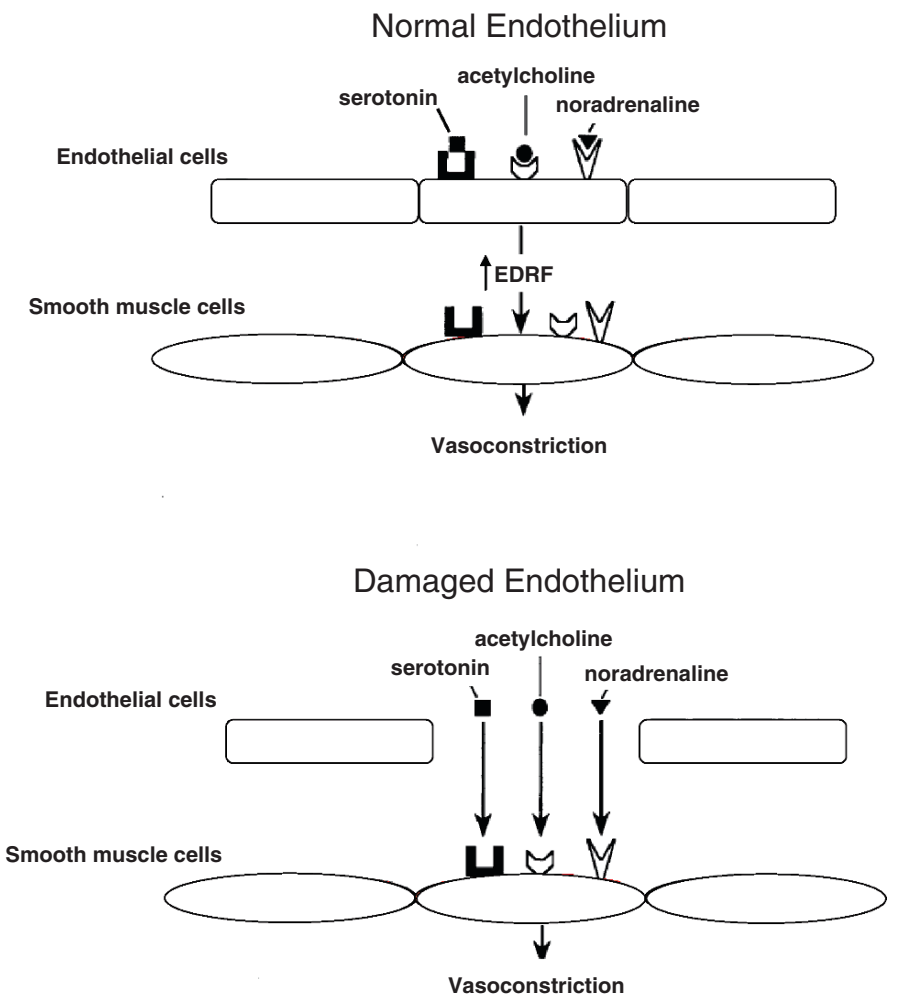

Fig. 5.2 *Top*: endothelial and smooth muscle cells in coronary vessels in the presence of intact endothelium. Mediators such as serotonin, acetylcholine, and noradrenaline stimulate the corresponding receptors present on the endothelial surface, which induce smooth muscle cell relaxation and vasodilation via EDRF release. *Bottom*: when endothelium is damaged, the same mediators act directly on the corresponding receptors present on the smooth muscle membrane, causing vasoconstriction

has complex dose-dependent effects on β_1-, β_2-, and α_1-adrenoreceptors [6], whereas the principal target of adenosine and dipyridamole are adenosine receptors, both A_1 and A_2, present both in myocardium and in coronary vessels [7]. In particular, stimulation of A_2a receptors produces marked dilation of coronary resistance vessels, determining arteriolar vasodilation, whereas A_2b receptors mediate vasodilation in conductance vessels. Myocardial A1 adenosine receptors mediate the negative chronotropic and dromotropic effects of

Table 5.1 Pharmacodynamics of dobutamine

	Receptor populations		
	α_1	β_1	β_1
Myocardium	Increased inotropy	Increased chronotropy, Increased inotropy	–
Vasculature	Vasoconstriction	–	Vasodilation

Table 5.2 Pharmacodynamics of adenosine and dipyridamole

	Receptor populations			
	A_1	A_2a	A_2b	A_3
Myocardium	Decreased chronotropy Decreased dromotropy Chest pain ? Preconditioning			
Vasculature		Coronary arteriolar vasodilation	Conductance vessel vasodilation	
Mast cells				? Bronchospasm ? Hypotension ? Preconditioning

adenosine and the direct algogenic effect. A_3 receptors are found on the surface of mast cells and may play a role in mediating bronchospasm and hypotension. Exogenous and endogenous adenosine may profoundly dilate coronary arterioles with minimal effect, if any, on systemic circulation, probably because A_2a receptors are more abundant in coronary arterioles than in any other vascular area [7]. A_1 and A_3 receptors also have a potential role in mediating preconditioning [7].

Adenosine is produced intracellularly via two pathways (Fig. 5.3), but it does not exert its effects until it leaves the intracellular environment and interacts with A_1 and A_2 adenosine receptors on the cell membrane [8]. As illustrated by the scheme in Fig. 5.3, dipyridamole acts by blocking the uptake and transport of adenosine into the cells, thereby resulting in a greater availability of adenosine at the receptor site. Both these mechanisms can provoke myocardial ischemia in the presence of a fixed reduction in coronary flow reserve due to organic factors (involving the epicardial coronary arteries and/or myocardium and/or microvasculature).

5.2 Increased Demand

This mechanism can be easily fitted into the familiar concept framework of ischemia as a supply–demand mismatch, deriving from an increase in oxygen requirements in the presence of a fixed reduction in coronary flow reserve. The different stresses can determine increases in demand through different mechanisms (Fig. 5.4).

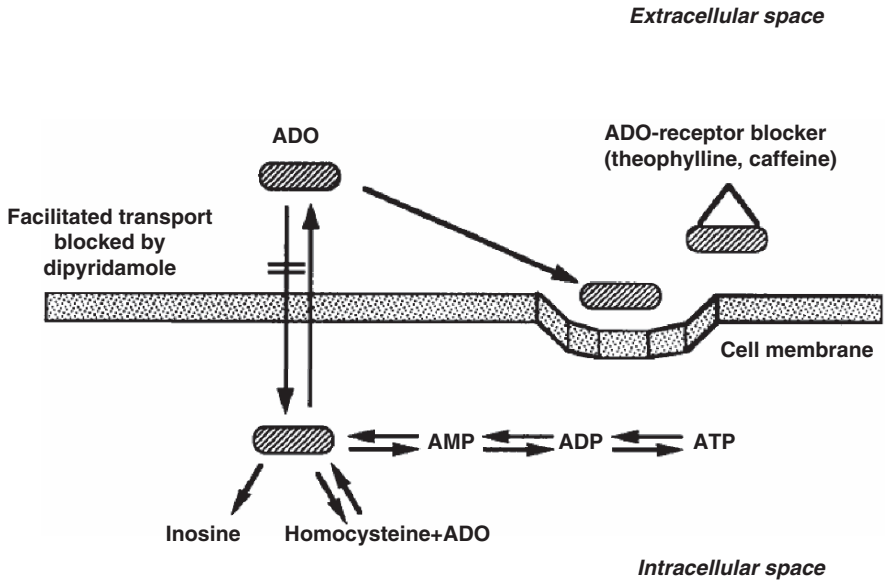

Fig. 5.3 Metabolism and mechanisms of action of adenosine in the coronary arteries. *ADO* adenosine, *AMP* adenosine monophosphate, *ADP* adenosine diphosphate, *ATP* adenosine triphosphate. (Modified from [8])

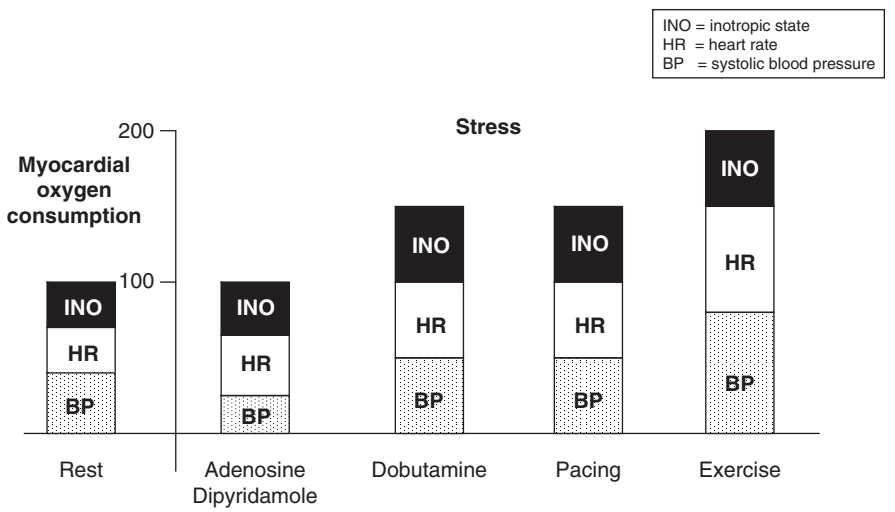

Fig. 5.4 Major determinants of myocardial oxygen consumption in resting conditions (*left*) and during some stresses (*right*) commonly employed with echocardiography. The relative contributions of systolic blood pressure, heart rate, and inotropic state to myocardial oxygen demand are represented. During dipyridamole or adenosine stress there is a mild increase in oxygen consumption, due to the increase in the inotropic state or heart rate, respectively. The rise in oxygen demand is even more marked during exercise, which causes an increased heart rate as well as increased inotropic state and systolic pressure. (Redrawn and modified from [9])

In resting conditions, myocardial oxygen consumption is dependent mainly on heart rate, inotropic state, and the left ventricular wall stress (which is proportional to the systolic blood pressure) [9]. Following dipyridamole or adenosine administration, a slight increase in myocardial function, a modest decrease in blood pressure, and mild tachycardia can be observed, overall determining only a trivial increase in myocardial oxygen demand [10].

During exercise, the increase in heart rate, blood pressure, and inotropic state accounts for the overall increase in myocardial oxygen consumption (Fig. 5.2) [11]. To a lesser degree, pacing and dobutamine also increase myocardial oxygen demand [12]. During pacing, the increase is mainly due to the increased heart rate. Dobutamine markedly increases contractility and heart rate (Fig. 5.2). Greater myocardial oxygen consumption due to heart rate increase occurs with the coadministration of atropine with dobutamine [13] and dipyridamole [14].

5.3 Flow Maldistribution

In the presence of coronary atherosclerosis, appropriate arteriolar dilation can paradoxically exert detrimental effects on regional myocardial perfusion, causing overperfusion of myocardial layers or regions already well perfused in resting conditions at the expense of regions or layers with a precarious flow balance in resting conditions [15].

In "vertical steal," the anatomical requisite is the presence of an epicardial coronary artery stenosis, and the subepicardium "steals" blood from the subendocardial layers. The mechanism underlying vertical steal is a fall in poststenotic pressure secondary to the increase in flow across the stenosis [16]. From the hydraulic viewpoint, it is well known that even in the presence of a fixed anatomical stenosis, resistance is not fixed. After administration of dipyridamole the arterioles dilate, thereby increasing flow across the stenotic lesion. This increased flow may lead to a greater drop in pressure, the magnitude of which is related to the severity of the stenosis and to the increase in flow. In the presence of a coronary stenosis, the administration of a coronary vasodilator causes a fall in poststenotic pressure, and therefore a critical fall in subendocardial perfusion pressure (Fig. 5.5), which in turn provokes a fall in absolute subendocardial flow, even with subepicardial overperfusion. In fact, the coronary autoregulation curve can be broken into two different curves (Fig. 5.5), with the subendocardium more vulnerable than the subepicardium to lowering of coronary perfusion pressure. Regional thickening is closely related to subendocardial rather than transmural flow, and this explains the "paradox" of a regional asynergy, with ischemia in spite of regionally increased transmural flow. Because endocardial oxygen demands are greater than epicardial ones, the resistance vessels of the endocardium are more dilated than those of the subepicardium, ultimately resulting in selective subendocardial hypoperfusion (Fig. 5.5).

"Horizontal steal" requires the presence of collateral circulation between two vascular beds (Fig. 5.6); the victim of the steal is the myocardium fed by the more stenotic vessel. The arteriolar vasodilatory reserve must be at least partially preserved in the

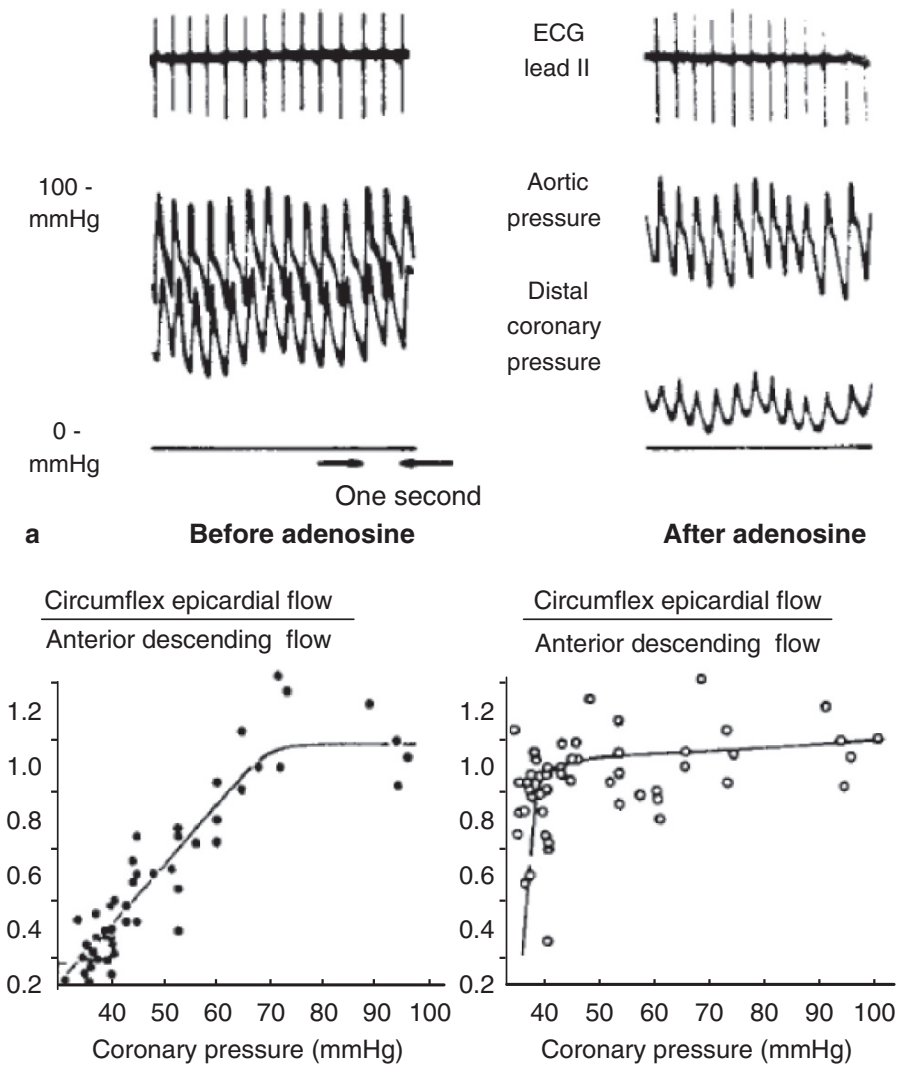

Fig. 5.5 *Upper panel*: The mechanisms of vertical steal, effect of adenosine infusion in an experimental model of severe coronary stenosis. (From [16]). *Lower panel*: Coronary autoregulation curve in the subendocardial and subepicardial layers. (From [17])

donor vessel and abolished in the vessel receiving collateral flow [17, 18]. After vasodilation, the flow in the collateral circulation is reduced relative to resting conditions, since the arteriolar bed of the donor vessel "competes" with the arteriolar bed of the receiving vessel, whose vasodilatory reserve was already exhausted in resting conditions (Figs. 5.6, 5.7).

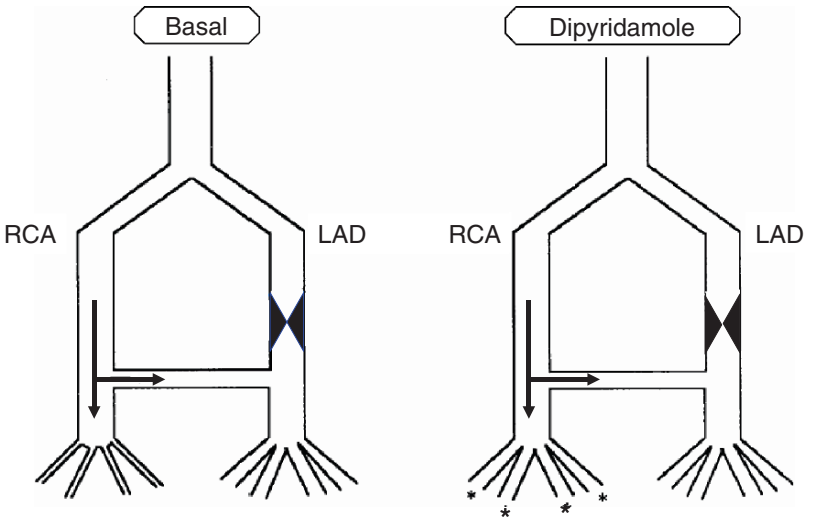

Fig. 5.6 Hydraulic model illustrating coronary horizontal steal. For this example, the right coronary artery (*RCA*) is the supply artery, with the vascular distribution of the severely stenotic left anterior descending (*LAD*) artery supplied by collaterals from the right coronary artery. Coronary steal following coronary arteriolar vasodilation refers to a decrease in absolute forward flow through collateral channels to the collateral-dependent vascular bed. With vasodilation of distal coronary arteriolar beds there is a flow-related drop in pressure along the supply artery. Therefore, distal perfusion pressure to the collateral vessels falls since collateral flow depends primarily on the driving pressure gradient (between distal perfusion pressure of the supply and collateralized vascular bed). (Redrawn and modified from [17])

The stresses provoking this flow maldistribution act through a "reverse Robin Hood effect" [19]; unlike the hero who stole from the rich to give to the poor [20, 21], they steal from the poor (myocardial regions or layers dependent on a critically stenosed coronary artery) and give to the rich (regions or layers already well nourished in resting conditions). The biochemical effector of this hemodynamic mechanism is the inappropriate accumulation of adenosine, which is the main physiological modulator of coronary arteriolar vasodilation. Inappropriate adenosine accumulation can be triggered either by a metabolic stimulus (such as exercise or pacing) or by a pharmacological one (such as exogenous adenosine or dipyridamole, which inhibits the cellular reuptake of endogenously produced adenosine) [22]. It is certainly difficult to quantify the relevance of flow maldistribution in inducing ischemia, but this mechanism is likely to play a key role in adenosine- or dipyridamole-induced ischemia and a relatively minor, although significant, role in exercise- or pacing-induced ischemia [20–23]. Theoretically, dobutamine might also induce a moderate degree of flow maldistribution by stimulating β-adrenergic receptors, which mediate coronary arteriolar vasodilation [24] (Fig. 5.8).

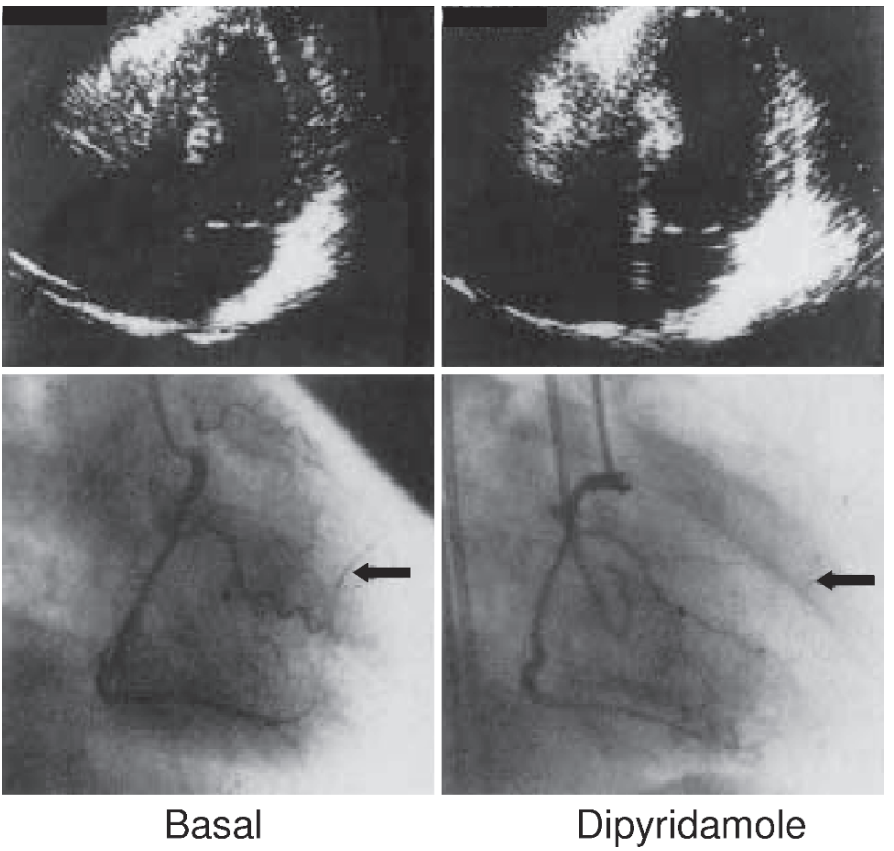

Fig. 5.7 An example in which collaterals were supplied by the right coronary artery to the occluded left anterior descending artery. Two-dimensional echocardiographic frames, taken at end-systole (*top*); and coronary angiographic images (*bottom*), obtained in basal conditions and after dipyridamole administration. After dipyridamole, the apex is dyskinetic; the coronary angiography shows almost total disappearance of the collateral vessels (*arrows*). (Modified from [15])

5.4 Exercise-Simulating Agents: Scientific Fact or Fancy Definition?

Among stresses, a currently used differentiation is between "exercise-simulating agents," such as dobutamine or arbutamine, and vasodilator stressors, such as dipyridamole or adenosine. It is important to emphasize that none of the pharmacological stresses are "exercise simulating" in a strict sense. Only exercise offers complex information not only on coronary flow reserve, but also on cardiac reserve and cardiovascular efficiency (i.e., how the coronary reserve is translated into external work). Coronary reserve and cardiovascular efficiency are codeterminants of exercise tolerance and therefore of

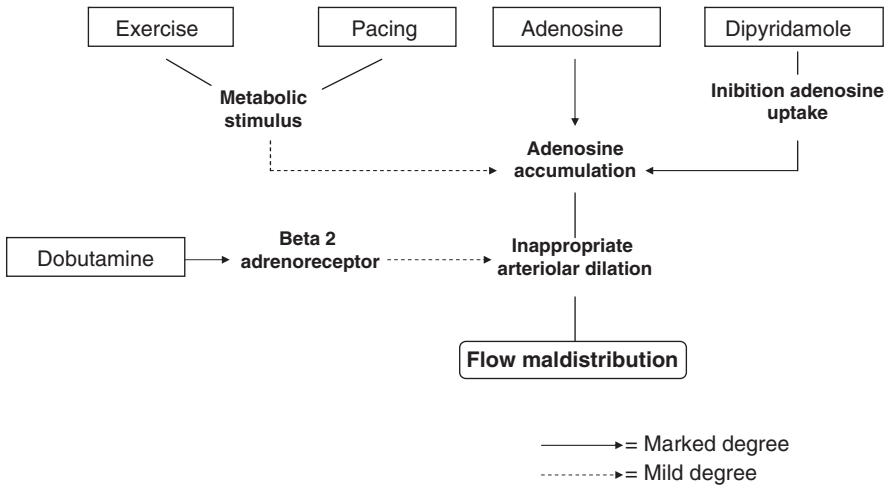

Fig. 5.8 The biochemical pathways leading to inappropriate arteriolar vasodilation under different stresses

the quality of life for the individual patient. No pharmacological stress can mimic the complex hemodynamic, neural, and hormonal adaptations triggered by exercise, nor can they offer information on cardiovascular efficiency. Exercise explores the entire physiological chain supporting external work: psychological motivation, central and peripheral nervous system, lungs, myocardium, coronary circulation, peripheral blood circulation and skeletal muscle, down to cell respiration and mitochondrial oxygen utilization [25]. Of this chain, pharmacological stresses only test the "coronary" ring. From the echocardiographic viewpoint, the mechanical pattern of stress-induced function increase differs between exercise and pharmacological stresses – including dobutamine, which affects regional wall function in a manner similar to atrial pacing rather than dynamic exercise [26]. From the clinical viewpoint, changes in rate–pressure product can stratify disease severity with exercise, not with pharmacological stresses. Antianginal therapy affects pharmacological stress results – and especially dobutamine results (as discussed in more detail in Chap. 18) in a manner largely unrelated to the effects of the same therapy on exercise. Finally, arrhythmias, heart rate, and blood pressure response enrich the diagnostic information obtainable with exercise stress testing, not with pharmacological testing. On the other hand, all stresses can be considered "exercise simulating" for the purpose of diagnosing coronary artery disease. Their mechanism of action is the extreme exaggeration of a biochemical and hemodynamic mechanism actually operating during exercise, such as adrenergic stimulation with dobutamine or adenosinergic stimulation with dipyridamole [20–22].

Last but not least, from a less physiological but more pragmatic point of view, all stresses should be considered exercise simulating since they induce ischemia with similar frequency, in the same region, and to a comparable degree as exercise. They also titrate the positive response, but the equivalent of the ischemic workload is the drug dose (the "pharmacological dose load") sufficient to elicit ischemia.

5.5 New Pharmacological Stresses

The family of pharmacological stresses is rapidly expanding, due to the combined pressure of scientific and economic motivations. In the family of catecholaminic stresses, arbutamine is characterized by a potent β-agonist effect, with a stronger chronotropic and a milder inotropic action than dobutamine. It might be considered conceptually similar to a pacing test, since it stresses the myocardium mainly through an increase in heart rate [27]. However, differently from pacing, arbutamine stress is noninvasive rather than semiinvasive; it is pharmacological rather than electrical; it is a flexible stress, tailored to the patient's response, rather than fixed and standard like electrical pacing. It is also highly expensive and no longer commercially available in most countries. For vasodilator stresses as well, new drugs are on the horizon, such as new selective adenosine A_2 receptor agonists with short half-lives [28].

5.6 The Atropine Factor in Pharmacological Stress Echocardiography

Atropine is a naturally occurring antimuscarinic drug consisting of an alkaloid of the belladonna plants. During the time of the Roman Empire the plant was frequently used to produce poison. This prompted Linnaeus to name the shrub *Atropa belladonna*, after Atrops, the eldest of the Three Fates, who cuts the thread of life. The name belladonna (i.e., "beautiful woman") derives from the alleged use of this preparation by Italian women to dilate their pupils [29]. Atropine is the prototype of antimuscarinic drugs, which inhibit the actions of acetylcholine on anatomical effectors innervated by postganglionic cholinergic nerves. The main effect of atropine on the heart is to induce tachycardia by blocking vagal effects on the M2 receptors on the seno-atrial nodal pacemaker. Atropine also enhances atrioventricular conduction, and for this reason it is usually given before pacing stress (see Chap. 14). Atropine-induced mydriasis may occasionally raise the intraocular pressure in patients with glaucoma, which is therefore a contraindication to atropine administration. Atropine also decreases the normal amplitude of bladder contraction, and severe prostatic disease is thus another contraindication to atropine administration. Finally, atropine reduces gastrointestinal tract motility and secretion and for this reason can be given before transesophageal stress. Administration of atropine on top of dobutamine [13] vasodilators [14–30], or exercise [31, 32] improves diagnostic sensitivity. Not surprisingly, however, the risk of resistant ischemia increases with atropine [33, 34], along with nonischemic side effects, including (as described in dobutamine plus atropine) atropine intoxication [35], consisting of restlessness, irritability, disorientation, hallucinations, or delirium, usually disappearing spontaneously over a few hours [2].

5.7 The Combined Stress Approach

The combined stress can be either dipyridamole–exercise or dipyridamole–dobutamine. Dipyridamole causes only a trivial increase in myocardial oxygen demand, provoking ischemia mainly through flow maldistribution phenomena triggered by endogenous

adenosine accumulation. The flow increase achieved by a high dipyridamole dose lasts for a relatively long time, remaining at plateau for about 30 min and, therefore, representing an ideal "flow maldistribution" background over which another stress can be superimposed. It has previously been shown that dipyridamole does not block the hemodynamic response of exercise [36] or dobutamine [37], and that it potentiates the ischemic potential of both exercise and dobutamine. The underlying hypothesis is that a stepwise increment of myocardial oxygen consumption – unable per se to elicit ischemia in the presence of mild coronary artery disease – might reach the critical threshold when the ischemic ceiling is lowered by concomitant flow maldistribution triggered by dipyridamole infusion [36] (Fig. 5.9). The clinical fact is that the combined stress test can detect anatomically milder forms of coronary disease missed by either test used separately [36–38].

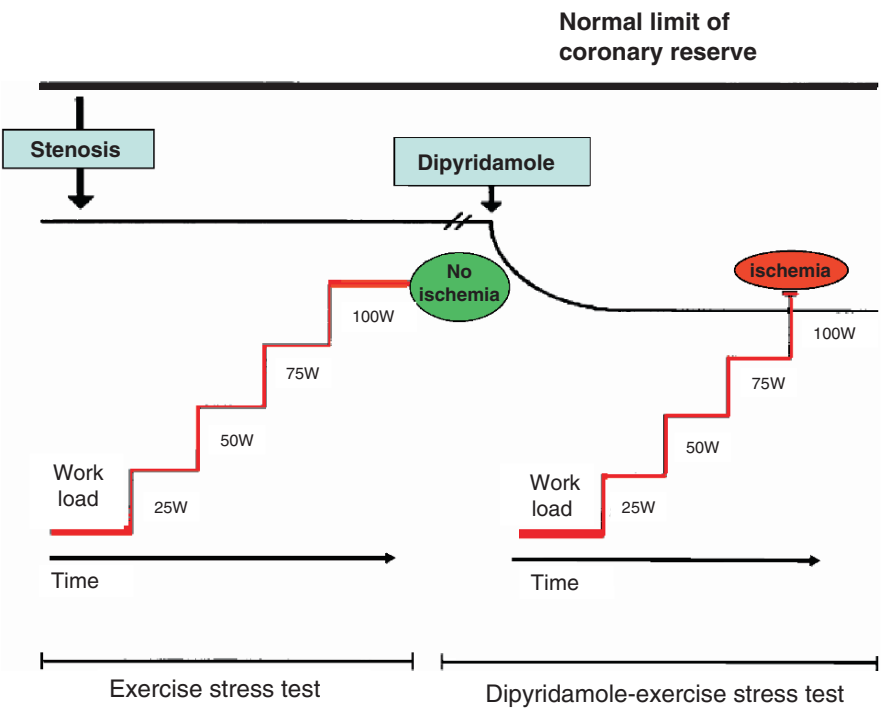

Fig. 5.9 Dipyridamole sensitization of the ischemic potential of exercise. Coronary stenosis (*thick arrow*) may permanently although not severely lower the maximal flow availability (coronary reserve), so that the myocardial ischemic threshold is not reached with an "ordinary" exercise stress test. With dipyridamole premedication (*thin arrow*), the hemodynamic response to exercise is not prevented (normal stepwise increase in workload), but the maximal flow availability is significantly lowered for the occurrence of flow maldistribution phenomena. (From [36] with permission)

5.8 Vasodilatory Power and the Hierarchy of Testing

Each of the prototype stresses for the detection of coronary artery disease can induce ischemia through either one of the two main pathophysiological pathways: "steal effect" (also named flow maldistribution) and increased oxygen demand (Fig. 5.10).

No stress is 100% "pure," since adenosine and dipyridamole also slightly increase heart rate, and exercise and dobutamine also induce a certain (mild) degree of flow maldistribution. Both families of stresses are more or less equally effective as ischemic stressors in the presence of significant coronary artery disease (Fig. 5.11). For a given ischemic diagnostic marker (for instance, regional wall motion abnormalities with stress echocardiography), sensitivity is higher for tests combining the two pathways (such as dipyridamole–exercise, dipyridamole–dobutamine, or dipyridamole atropine) when compared with tests based on one pathway (dipyridamole or dobutamine or exercise) alone. The relevance of the steal effect is also directly mirrored by the stress capacity to recruit coronary flow reserve. Adenosinergic stresses are ideally suited for this, since – unlike dobutamine or exercise associated with a threefold flow increase – they determine a fivefold increase in coronary blood flow with a full recruitment of pharmacological flow reserve [39]. The greater the vasodilation, the higher the potential for inappropriate steal phenomena in the presence of coronary artery disease. In recent years, the two different sides of the coin of the stress test, vasodilatory and ischemic stress, merged in the dual imaging of coronary flow reserve and wall motion during vasodilatory stress echocardiography [40–42].

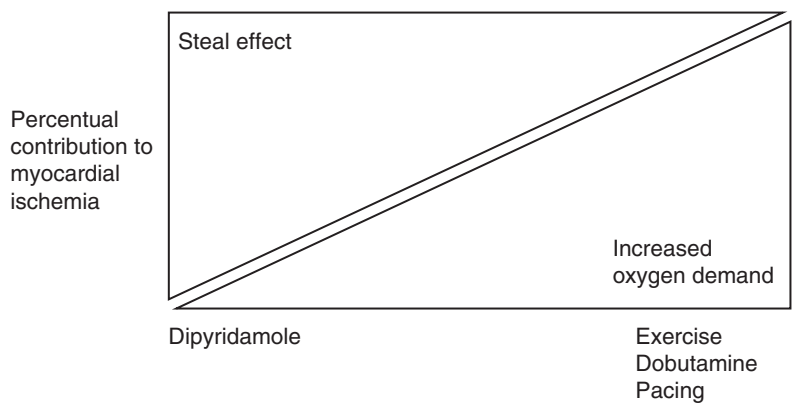

Fig. 5.10 Conceptual allocation of tests employed in combination with echocardiography to detect coronary artery stenosis inducing ischemia via steal effect (*left*) or increased myocardial oxygen demand (*right*), or both mechanisms

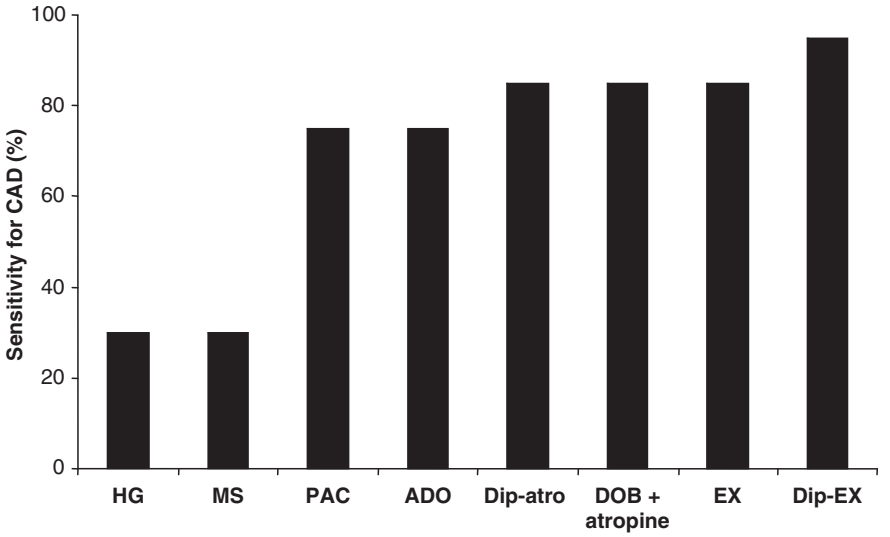

Fig. 5.11 The hierarchy of test sensitivity for the diagnosis of coronary artery disease. The sensitivity is highest for tests combining the two main mechanisms of increased oxygen consumption and steal phenomena. On the *far left* of the *x-axis*, tests that are below the threshold of clinical value, such as handgrip and mental stress. *Dip-Ex* dipyridamole exercise, *Dip* dipyridamole, *Ado* adenosine, *HG* handgrip, *MS* mental stress, *PAC* pacing

5.9 The Fosbury Flop and the Classic Straddle in the Stress Echocardiography Laboratory

The use of stress to increase myocardial oxygen demand in order to provoke ischemia is like the classic straddle method in the high jump: it is conceptually familiar to everybody (everyone has tried it at least once) and it is pushed forward by the force of tradition. The steal effect is like the "Fosbury flop": it is more recent, may appear counterintuitive, but works at least as well as the straddle method. As a young high jumper in the early 1960s, Dick Fosbury had trouble mastering the standard technique, called the straddle, so he began doing the high jump by approaching the bar with his back to it instead, doing a modified scissor kick and going over the bar backwards and horizontal to the ground. As goofy as it looked, it worked. Similarly, as strange as it may look within the supply–demand mismatch framework, the concept of inducing ischemia through a vasodilator instead of by increasing myocardial oxygen demand has worked. Fosbury caused a sensation when he won the gold medal in the 1968 Olympics. The Fosbury flop has since become a standard technique for high jumpers – whether Olympic champions pushing forward the limits of the specialty, or lazy, fat, chubby kids trying to satisfy the coach in gym class at elementary

school. Twenty years after the initial proposal in 1985, vasodilatory stress echocardiography is the convenient option for primary care stress echocardiographers, who will benefit from a stress that pollutes the image quality very little, reducing the problems of interpretation. It is also a good option for stress echocardiographers with top level expertise and technology, since it allows one to combine wall motion and coronary flow imaging in the same stress [40, 41]. Dual imaging is currently recommended by European guidelines as the state-of-the-art approach along with pharmacological stress echocardiography [42]. The force of innovation sets new standards – impossible to accept if one ignores the pathophysiological basis of the technique.

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