Pharmacology & Therapeutics 140 (2013) 121–132

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Associate editor: Y.S. Chatzizisis

Pharmacologic manipulation of coronary vascular physiology for the evaluation of coronary artery disease

Hoshang Farhad [a,b], Venkatesh L. Murthy [c,d,*]

[a] Cardiovascular Imaging Program, Department of Internal Medicine, Cardiovascular Division, Brigham & Women's Hospital, Boston, MA, USA
[b] Cardiovascular Imaging Program, Department of Radiology, Brigham & Women's Hospital, Boston, MA, USA
[c] Division of Cardiovascular Medicine, Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA
[d] Division of Nuclear Medicine and Cardiothoracic Imaging, Department of Radiology, University of Michigan, Ann Arbor, MI, USA

ARTICLE INFO

Keywords:
Coronary artery disease
Stress testing
Exercise
Vasodilators
Inotropic agents
Atherosclerosis

ABSTRACT

During the last forty years tremendous progress has been made in our understanding of coronary atherosclerosis and in the development of methods to characterize atherosclerotic disease burden and risk. Stress testing is designed to elucidate abnormalities in myocardial perfusion during stress due to abnormal coronary vasomotor response. We summarize the underlying determinants of normal coronary vasomotor tone as well as its responsiveness to both exercise and pharmacologic stressors. We introduce the various methods of assessing the presence of myocardial ischemia. A detailed discussion of the most commonly used stress agents as well as their clinical advantages and limitations follows.

Contents

1. Introduction

Coronary artery disease (CAD) remains the leading cause of death worldwide (Department of Health Statistics and Information Systems, 2012; Laslett et al., 2012). Because a variety of therapies have proven benefit for reduction of risk of myocardial infarction and death from cardiac causes (Ridker et al., 1991; Scandinavian Simvastatin Survival Study Group, 1994; Shepherd et al., 1995; Antithrombotic Trialists' Collaboration, 2002; Gibbons et al., 2003; Ridker et al., 2008; Smith et al., 2011), early diagnosis of CAD and effective risk stratification is critical (Gibbons et al., 1999, 2003). However, because the clinical manifestations and symptoms of CAD are varied and overlap with many other conditions, diagnosis based on history and physical examination alone is challenging (Diamond & Forrester, 1979). Cardiac stress testing, which is designed to identify areas of regional myocardial hypoperfusion or ischemia, is currently the most widely used non-invasive diagnostic method for CAD today. A large number of protocols for stress testing have been developed and validated. Generally they combine a stressor, usually exercise or a pharmacologic alternative, and an ischemia readout, which may range from simple electrocardiography (ECG) to imaging modalities such as cardiac ultrasonography (echocardiography), nuclear myocardial perfusion imaging or advanced imaging modalities such as cardiac magnetic resonance imaging (MRI) and computed tomography (CT). This article reviews the pharmacology of clinically used stress agents, including exercise, and their applications.

2. Coronary vascular physiology

Coronary vascular tone results from a balance between factors promoting vasoconstriction and those promoting relaxation. Perhaps

* Corresponding author at: 1338 Cardiovascular Center, 1500 E. Medical Center Dr, SPC 5873, Ann Arbor, MI 48109, USA. Tel.: 734 936 5387; fax: 734 232 3246.
E-mail address: vlmurthy@med.umich.edu (V.L. Murthy).

0163-7258/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pharmthera.2013.06.004

the most physiologically central among these is nitric oxide (NO) (Marín & Rodríguez-Martínez, 1997). Originally identified as the endothelium-derived relaxing factor (Furchgott, 2003), its production is catalyzed by several enzymes from the amino acid L-arginine (Moncada & Higgs, 1993). Because NO is a freely diffusible gas, it is able to transit the subendothelial space into vascular smooth muscle cells. There, it reacts with heme-bound iron in guanylate cyclase in vascular smooth muscle cells causing increased 3,5-cyclic guanosine monophosphate (cGMP) which in turn results in smooth muscle relaxation and vasodilation (Moncada & Higgs, 1993).

In addition to muscarinic stimulation by acetylcholine (the first vasodilator found to function in a NO-mediated endothelium-dependent manner), the vasodilator effects of adenosine triphosphate (ATP), adenosine diphosphate (ADP), substance P, bradykinin, histamine, thrombin, serotonin and vasopressin also all occur through NO (Furchgott, 2003). In the setting of endothelial dysfunction due to aging (Zeiher et al., 1993; Celermajer et al., 1994; Gerhard et al., 1996), hypertension (Zeiher et al., 1993; Antony et al., 1994; Nitenberg et al., 1995; Alexánderson et al., 2012), dyslipidemia (Zeiher et al., 1993), smoking (Campisi et al., 1998; Iwado et al., 2002), glucose intolerance (Quiñones et al., 2004; Prior et al., 2005) or other factors, normal vasodilator response may be reduced, absent or even replaced by paradoxical vasoconstriction (Ludmer et al., 1986). For example, sympathetic activation leads to endothelium dependent coronary vasodilation via activation of β-receptors (Ray et al., 1999). However, in the presence of endothelial dysfunction, sympathetic activation by cold-pressor testing leads to vasoconstriction (Nabel et al., 1988) by direct activation of α-adrenergic receptors on coronary vascular smooth muscle cells.

Endothelium-independent vasodilators such as nitroglycerin and sodium nitroprusside act directly on vascular smooth muscle, stimulating guanylate cyclase and cGMP production. However, arteriolar vasodilation by nitrate administration leads to increased flow and endothelial shear stress in larger conduit vessels which supply the arterioles. This subsequently leads to endothelium dependent vasodilation of the conduit vessels, in this case the epicardial coronary arteries (Nabel et al., 1990). In this sense, in normal individuals, endothelium dependent vasodilation contributes to increased blood flow caused by "endothelium-independent" vasodilators.

Increased metabolic demand from exercise results in vasodilation of arteries supplying active skeletal muscles. Increased sympathetic activation leads to splanchic vasoconstriction and venoconstriction, diverting blood flow from digestion and increasing venous return. Withdrawal of vagal parasympathetic tone leads to an initial increase in heart rate. Sympathetic stimulation also leads to further increased heart rate (chronotropy) and also augmented contractility (inotropy). Because there is generally little reserve capacity for increased cardiac oxygen extraction from blood (Messer et al., 1962; Holmberg et al., 1971; Nelson et al., 1974; Feigl, 1983), increased cardiac work that results from chronotropic and inotropic stimulation requires increased myocardial blood flow. During exercise, this is principally mediated by stimulation of β_2-adrenergic receptors in the coronary vascular endothelium (Ray et al., 1999), predominantly in the arterioles (Muntz et al., 1984).

In addition to feed-forward control through the β-adrenergic system (Miyashiro & Feigl, 1993), metabolites exert feed-back control on coronary tone (Miyashiro & Feigl, 1995). Adenosine, the principal among these, is an endogenous nucleoside which is formed by degradation of adenosine triphosphate (ATP) in the setting of an imbalance between oxygen supply and demand (Shryock & Belardinelli, 1997) such as during myocardial ischemia (Borst & Schrader, 1991). Because adenosine acts to increase coronary blood flow and decrease cardiac conduction and systemic blood pressure, it has been called a "retaliatory metabolite" in that it acts to ameliorate the adverse conditions which promote its formation (Newby, 1984). Recent work has demonstrated that while the coronary vasodilatory effect can largely be ascribed to activation of adenosine A2A receptors (Belardinelli et al., 1998), activation of adenosine A2B receptors may also have a role (Morrison et al., 2002; Berwick et al., 2010). Although adenosine induces endothelium-mediated, NO-dependent vasodilation of epicardial coronary arteries (Vials & Burnstock, 1993; Iwamoto et al., 1994; Abebe et al., 1995) and the microvasculature (Lynch et al., 2006), much of the effect is likely mediated by arteriolar vasodilation, which involves both endothelial NO-dependent pathways and direct action on ATP-sensitive potassium channels in arteriolar smooth muscle (Hein et al., 1999; Berwick et al., 2010), although the degree of endothelial-dependence may be limited in humans with coronary atherosclerosis (Sato et al., 2005). This is supported by the finding that the degree of epicardial coronary arterial diameter increase is strongly related to the blood flow velocities (Lupi et al., 1997), suggesting that epicardial coronary artery dilation is through a flow-mediated endothelium-dependent mechanism (Rubanyi et al., 1986).

3. Effects of coronary artery disease

A robust auto-regulatory system maintains myocardial perfusion across a wide spectrum of conditions ranging from rest to high level exercise (Klocke, 2007). Furthermore, in early to mid-stage atherosclerosis, plaques may remodel outwards (Glagov et al., 1987), decreasing their hemodynamic significance (Gould, 2009). Although these adapatations are able to preserve resting perfusion even in the presence of moderate to severe coronary stenoses, vasodilator capacity is impaired resulting in reduction in blood flow at stress (Uren et al., 1994; Di Carli et al., 1995). Consequently, maneuvers to increase myocardial perfusion and/or oxygen demand are generally required to provide adequate sensitivity for CAD in stable patients, especially those whose symptoms are generally only present with exertion or other stressors.

Impaired vasodilation of atherosclerotic vessels (especially those with moderate-severe disease) during stress may result in relative hypoperfusion and, in severe cases, ischemia in the subtended territories. Generally, the results of myocardial hypoperfusion occur sequentially in an ischemic cascade (Serruys et al., 1984; Sigwart et al., 1984; Serruys et al., 1989) beginning with hypoperfusion itself without overt cellular consequences, followed by lactic acid production from anaerobic metabolism, myocardial stiffening due to impaired relaxation, regional and/or global systolic dysfunction, ST segment abnormalities on surface ECG recordings and finally clinical symptoms such as chest pain and dyspnea (Fig. 1). A critical early step in this pathway is impairment in calcium handling. Ischemia leads to rapid accumulation of intracellular calcium which has several adverse consequences including slowed conduction in the ischemic zone (Venkataraman et al., 2012) and ectopic activity (Pumir et al., 2005). These, in turn, are believed to promote the development of ventricular arrhythmias seen among patients with ischemia (Furukawa et al., 1991; Wolfe et al., 1991).

4. Ischemia readouts

As discussed, the effects of myocardial ischemia are manifold, ranging from metabolic changes at the cellular and molecular level to regional and global systolic dysfunction. A variety of the manifestations of myocardial hypoperfusion and ischemia can be used individually and in combination to evaluate the presence of impaired coronary vasomotor response (Table 1). Selection among these depends upon the clinician's pre-test evaluation of the probability of coronary artery disease, patient factors which may limit or contraindicate certain choices, local expertise and equipment availability, as well as cost.

4.1. Perfusion methods

Hypoperfusion represents the first step of the ischemic cascade and can be present in the absence of molecular and cellular changes