Regulating myocardial blood flow in health and disease is a complex, multifaceted process. The objective of this article is to outline for the practicing clinician a basic set of principles necessary for understanding important control mechanisms operative under normal physiologic conditions and in selected common disease states. Classical and newer insights into the process of myocardial blood flow regulation are reviewed. An improved understanding of these control mechanisms will enhance the clinician's ability to diagnose and treat abnormalities of the coronary circulation associated with such common clinical conditions as ischemic heart disease, diabetes, dyslipidemia, hypertension, and congestive heart failure.

Introduction
Regulating myocardial blood flow in health and disease is a complex, multifaced process. A comprehensive review of the subject, therefore, is beyond the scope of this article. Accordingly, an effort is made to focus on fundamental concepts that will provide a useful framework for understanding the physiology of the coronary circulation, in health and selected disease states, which will be particularly relevant to the practicing physician.

Regulating Myocardial Blood Flow in the Normal Coronary Circulation Overview
The heart, as with any other pump, requires energy to perform mechanical work. This energy is derived from adenosine triphosphate (ATP), which the myocardium synthesizes via two principal processes: oxidative metabolism of glucose and β oxidation of free fatty acid [1]. These two processes occur in the mitochondria and are critically dependent on oxygen for normal functioning. Myocardial oxygen supply is largely a function of myocardial blood flow because the capacity of the myocardium to extract oxygen from the blood is nearly maximal (60% to 80%) at rest and so any increase in oxygen requirement, typically to do more work, must be met by an increase in myocardial blood flow [2,3]. Thus, a cardinal principle of the physiology of the normal coronary circulation is that myocardial blood flow is regulated to meet the prevailing level of myocardial oxygen demand. This function is crucial because deprived of oxygen, myocardial contraction quickly ceases, and if persistent for more than 15 to 30 minutes, infarction ensues.

Determining Myocardial Oxygen Demand
Most oxygen consumed by the heart (MVO₂) is required for contraction [4]. Only a small amount (~ 20%) is needed for basal requirements [5]. Further, under basal conditions, pressure work done by the heart (ie, generation of tension) consumes roughly four times the oxygen needed for volume work (shortening against load) and so is far more costly in terms of MVO₂ [5]. Substrate utilization also has an impact on MVO₂. Thus, to produce a mole of ATP exclusively by β oxidation of free fatty acid (eg, palmitate) requires about 13% more oxygen than aerobic metabolism of glucose. This is required because one glucose molecule yields 38 ATP with consumption of six oxygen (0.16 O₂/ATP) in comparison with 129 ATP from 23 oxygen (0.18 O₂/ATP) for one palmitate [6].

The principle determinants of myocardial oxygen demand are heart rate, myocardial contractility, and left ventricular (LV) preload and afterload. The latter two factors are interrelated because LV afterload is best described by LV wall tension (T), which traditionally is modeled by the Laplace equation (T = P*r/h), where P = intracavitary pressure, r = chamber radius, and h = wall thickness. Although LV afterload is commonly equated with systolic arterial pressure, systolic wall tension is a more accurate measure because it incorporates wall thickness. LV preload is a function of LV end-diastolic volume (LVEDV) and thus directly influences chamber radius, a determinant of LV afterload. Clinically, LVEDV generally is approximated by pulmonary capillary wedge pressure (PCWP), although for several reasons, notably alterations
in LV diastolic pressure/volume relations (relaxation and compliance), PCWP may not provide an accurate estimate of LVEDV. Myocardial contractility is the most difficult parameter to estimate clinically because there is no simple, load-independent, noninvasive index for it. The best available model is given by a series of LV end-systolic pressure volume points that form a straight line, whose slope (end-systolic elastance [Ees]) defines a given level of myocardial contractility [7]. The line becomes steeper when contractility increases and flatter with myocardial depression. The ratio of systolic arterial pressure to LV end-systolic volume has been used as a clinical approximation of Ees.

Changes in contractility generally produced directly proportional changes in MVO₂. In contrast, the manner in which heart rate, preload, and afterload are changed may not result in proportionate changes in MVO₂. Thus, atrial pacing, which artificially elevates heart rate without change in contractility, will augment MVO₂ much less than if heart rate is increased by an intervention that also augments contractility (e.g., catecholamine stimulation). Similarly, the manner in which LV systolic wall tension is altered (i.e., preload vs afterload) has an important influence on MVO₂. Augmentation of intracavitary pressure (pressure load) by a given percent generally will result in a proportionate increase in MVO₂. In contrast, a similar percentage increase in chamber volume alone (volume load) results in a much smaller relative increase in MVO₂. Thus, as noted above, imposition of a pressure load is much more costly in terms of MVO₂ (~ fourfold) than that of a proportionately similar increase in volume load.

Control mechanisms

The schema outlined above, more formally known as the metabolic theory of myocardial blood flow regulation (Fig. 1) [2], although certainly not the only one, is arguably the most relevant from the clinical care point of view. The exact signal(s) and detailed mechanism(s), which in the normal coronary circulation match myocardial blood flow (oxygen supply) to myocardial oxygen demand, have been topics of keen interest and intense study for more than 40 years [8,9]. In the normal coronary circulation, large, epicardial conductance vessels (i.e., the major coronary arteries and their branches visualized in coronary arteriograms) account for only a small fraction of resistance to flow, and most resistance is in the coronary microcirculation in arterioles less than approximately 200 μm in diameter [10]. Further, differences in relative responsiveness to various stimuli among different-sized vessels of this class have been reported by Chilian [10] and potentially add another complex layer to the overall regulation of myocardial blood flow. Nonetheless, for the purpose of this article, it is important to emphasize that the key locus of flow control is at the level of the coronary microcirculation in health and in many respects in disease states as well.

Factors capable of acting on the endothelium or smooth muscle (or both) of coronary microvessels are numerous (e.g., ATP, adenosine, nitric oxide [NO], endothelium-derived hyperpolarizing factor, prostaglandins, pO₂ [partial pressure of oxygen], pCO₂ [partial pressure of carbon dioxide], pH, endothelins, and reactive oxygen species [ROS]) [2,3,11••]. Adenosine has long been thought to be the mediator of coronary arteriolar tone [8,9]. A family of adenosine receptors has been described in recent years (A₁, A₂A, A₂B, A₃), with the A₂A receptor thought to be primarily responsible for mediating coronary vasodilation [11••]. Adenosine binding to its A₂A receptor has been shown to stimulate ATP-sensitive potassium channels (Kₑ₄) on endothelial and vascular smooth muscle and thereby enhances NO release (endothelium) and hyperpolarization of vascular smooth muscle mem-

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**Figure 1.** A simplified model of the metabolic theory of myocardial blood flow (MBF) regulation. Exercise induces catecholamine release and stimulates myocardial metabolism, which lowers tissue oxygen tension, the signal initiating compensatory vasodilation. Both cGMP and Kₑ₄ potassium channels play an important role in inducing vascular smooth muscle relaxation. This increases MBF and oxygen delivery to the myocardium, which restores tissue oxygen tension toward baseline, a classical feedback control system. Although considerably more complex, the schema serves as a useful starting point for understanding metabolic control of the coronary circulation. ATP—adenosine triphosphate; EDHF—endothelium-derived hyperpolarizing factor; NO—nitric oxide; pCO₂—partial pressure of carbon dioxide; pO₂—partial pressure of oxygen; RBC—red blood cell.