Brief Review

Regulation of Large Coronary Arteries

Mark A. Young and Stephen F. Vatner

The majority of studies on the control of coronary artery vasoactivity have examined changes in coronary blood flow and coronary vascular resistance, indices that primarily reflect regulation of small arterioles and precapillary vessels. With the emergence of coronary artery vasospasm as a significant cause of angina pectoris, myocardial infarction, and sudden death, the control of large coronary artery caliber has assumed more significance. It is clear that resistance coronary vessels and large coronary arteries differ in response to both pharmacologic and physiologic stimuli. Vasodilation of large coronary arteries may occur by direct action of agents on the arterial smooth muscle or by the indirect action of receptor occupation, changes in blood flow, or liberation of endothelial factors. These indirect factors appear to contribute also to responses to agents that constrict coronary smooth muscle directly or through the autonomic nervous system. Furthermore, the mechanisms responsible for control of large coronary vessels in the normal circulation are likely to be profoundly different from those in the presence of diseased vessels. For example, several factors associated with coronary artery disease — elevated plasma cholesterol levels, endothelial disruption, atherosclerosis, vascular stenosis, and aggregated platelets — all have important actions on the control of large coronary arteries. (Circulation Research 1986;59:579-596)

Historically, the large epicardial coronary arteries have been considered to serve only as conductance vessels, with the primary regulation of coronary vascular resistance limited to the smaller arterioles and precapillary vessels. Studies examining the regional distribution of coronary resistance between large and small coronary vessels have demonstrated that only 2-5% of total coronary resistance is contributed by the large epicardial coronary arteries under normal conditions, and that the large vessels contribute significantly to total coronary resistance only during maximal vasodilation or in the presence of a stenosis. These early studies also demonstrated profound dilation of large coronary arteries in response to administration of nitroglycerin. Dilation of the large coronary arteries and collateral channels would provide enhanced blood flow to the ischemic myocardium and thus account in part for the therapeutic action of the nitrate vasodilators during episodes of angina pectoris.

While these early studies were instrumental in describing the changes in epicardial coronary vessels, the concept of large coronary vascular control is changing. Recent technical advances have enabled more detailed study of the distribution of resistances in the coronary circulation. Chilian et al have demonstrated that approximately 25% of resting coronary vascular resistance can be attributed to vessels larger than 200 μm, and 50% to vessels larger than 100 μm. Such measurements of microvascular pressures and resistances will give a more complete assessment of resistance changes throughout the coronary vascular bed and will necessitate a more definite distinction between "large" and "small" coronary vessels. For the purposes of this review, large coronary arteries pertain to the major epicardial coronary arteries, using an anatomical localization. Traditionally, the term small coronary artery has referred to vessels, i.e., arterioles, which contribute to changes in coronary blood flow and total coronary resistance. This distinction will be used throughout this review. However, it should be noted that some studies have reported segmental differences in function of vessels isolated from different portions of the epicardial coronary arterial bed.

The emergence of coronary artery vasospasm as an important cause of angina pectoris, myocardial infarction, and sudden death has recently focused increased attention on the mechanisms responsible for control of large coronary artery tone. In view of the number of reports that suggest segmental differences in the response of coronary arteries to vasoactive agents, along with the widespread interest in the pathogenesis of coronary artery vasospasm, it is important to distinguish the mechanisms controlling the large vessels. This is especially true of the mechanisms that are altered in certain pathologic states and may therefore contribute to the abnormal vasoconstriction associated with spasm. While other recent comprehensive reviews of the coronary circulation have focused primar-
ily on the control of resistance vessels and control of vascular smooth muscle tone in general. The purpose of this article is to review the current understanding regarding the regulation of smooth muscle of large coronary arteries. While this review will focus on the control of large coronary vessels, pertinent observations from other vascular beds will also be included.

The techniques used to assess control of large coronary artery smooth muscle vary widely from isometric tension recording in isolated vessel segments to isolated perfused segments in situ, isolated perfused hearts, sonomicrometry of intact arteries, and angiographic measurement of coronary diameter. It is important to keep in mind when considering the literature discussed here that an understanding of the control of large coronary vessels must first make use of the detailed, mechanistic studies performed in isolated vessels, as well as include verification of the significance of these mechanisms in the intact conscious animal. In this connection, our laboratory has developed techniques for ultrasonic measurement of large coronary arterial caliber in conscious animals. This model offers the advantages of direct, instantaneous, and continuous on-line measurement of large vessel caliber in combination with measurements of coronary artery perfusion pressure, coronary blood flow, and left ventricular function. It has been implemented by several groups to elucidate large coronary artery control mechanisms in vivo, which have contributed significantly to elucidating vasoactive phenomena in large coronary arteries. It should be pointed out that each method measuring large coronary reactivity has particular disadvantages. For example, isolated vessels may not respond like in vivo vessels. Secondly, angiographic measurement of in situ vessels yields only temporary, transient visualization of coronary artery caliber, in addition to the problem that contrast media are vasoactive. While these concerns are alleviated with direct sonomicrometry, techniques for direct chronic measurement of vascular diameter have been criticized on the basis that implantation of transducers may cause vascular denervation, perivascular fibrosis, and damage to smooth muscle layers that will affect vasoactivity. For example, Dolezel et al reported that dissection and placement of an acrylic sleeve around the left anterior descending coronary artery in dogs produced perivascular scarring as well as local vascular and distal cardiac denervation. In contrast, Knight et al examined the effect of flow probe placement on the left circumflex coronary artery and reported no loss of cardiac innervation distal to the flow probe. Neither of these studies examined in detail the morphologic changes of the large artery, nor did they assess large artery vasoactivity. In this regard, Vatner et al reported no histological alterations of the circumflex coronary artery following implantation of ultrasonic dimension crystals, while demonstrating that both vasoconstrictor and vasodilator mechanisms were still intact.

Large coronary arteries are in general structurally similar to other muscular arteries and consist of three main layers. The inner, or intimal, layer lining the lumen consists of a single layer of endothelial cells, a subendothelial basement membrane, and the internal elastic lamina made up of elastic fibers. The second, or medial, layer contains the smooth muscle of the wall, which is responsible for the vasomotion of the vessel. This layer of smooth muscle cells is bound by the internal elastic lamina and by an external elastic lamina that separates the media from the adventitial, or outermost, layer of the vessel, composed primarily of collagen and elastin fibers. It is this layer that carries with it the majority of both sympathetic and parasympathetic nerves. While the structure of the coronary artery is generally similar to other muscular arteries, there are some minor differences. The intima is slightly thicker than that of other muscular arteries. It has a relatively high water content, the cell volume is low compared with other arteries of similar size, and, while the total connective tissue content is similar to other vessels, the coronary artery has the highest collagen to elastin ratio. Coronary vessels are also specialized in that they possess longitudinally oriented smooth muscle cells, which may, in addition to the circumferential fibers, contribute to the regulation of coronary vascular caliber. Yet the structure of coronary arteries is known to vary between species as well as between different coronary arteries in a single heart. While few studies have conducted detailed analyses comparing relative structure and function of different coronary arteries, it has been suggested that certain peculiarities of the coronary artery may be partly responsible for a tendency toward spasm. For example, Levicky and Gerova have suggested that a relatively thin wall and lack of elastic skeleton in the canine ventral intraventricular branch of the left coronary artery may promote luminal closure during contraction of the smooth muscle. Conversely, MacAlpin has reviewed geometric considerations of coronary arteries in the genesis of occlusion, and concluded that increases in wall thickness due to atherosclerotic disease will promote luminal closure during smooth muscle contraction. Clearly, the role of coronary vascular architecture in development of abnormal vascular reactivity and spasm needs further study.

The similarity of the aortic pressure and coronary diameter waveforms of a quiescent artery in situ indicate that, at rest, coronary caliber is passively determined by the connective tissue elastic properties. Nevertheless, activation of coronary vascular smooth muscle is capable of significantly altering the elastic behavior of the coronary artery. For example, Vatner et al and Pagani et al have demonstrated that activation of \( \alpha \)-adrenoceptors with methoxamine reduced the elastic wall modulus at any given arterial pressure and level of wall stress, indicating that coronary smooth muscle is capable of maintaining arterial elasticity constant in the face of changing pressure loads. The mechanical behavior of vascular smooth muscle is reviewed in detail by Gow and Cox.

Coronary vascular smooth muscle cells have a resting membrane potential of approximately \(-55 \text{ mV}\).
These cells are electrically inexcitable and do not produce action potentials in situ. Furthermore, they do not appear to possess fast sodium membrane channels such as found in cardiac muscle. Thus, changes in membrane potential are due mainly to alterations in potassium and calcium currents. Changes in membrane potential do, however, result in changes in contractile tension of vascular smooth muscle cells. Depolarization is associated with an increase in resting tension, and hyperpolarization is associated with relaxation, although changes in tension of vascular smooth muscle can occur without simultaneous changes in membrane potential. Changes in tension of vascular smooth muscle associated with depolarization result from calcium influx through so-called "potential-dependent" calcium channels. On the other hand, tension generated in the absence of depolarization results from influx calcium through "receptor-dependent" calcium channels. The relative dependence of vascular smooth muscle tension on extracellular calcium and intracellular calcium can explain the effectiveness of drugs that inhibit calcium influx in relaxation of coronary vascular smooth muscle.78,35 The relation between structure and function of vascular smooth muscle and coronary arteries, in particular, has been reviewed more comprehensively in recent publications.38,39

1. Mechanisms of Vasodilation

Historically, a paradox existed between results of in vitro and in vivo studies on the role of acetylcholine. In isolated blood vessel preparations, acetylcholine induces vascular constriction61,62 but in vivo elicited substantial vasodilation.45-46 Recently, this paradox was resolved by Furchgott and Zawadski27 who demonstrated that the ability of acetylcholine to dilate blood vessels depended upon an intact endothelial cell layer. This important observation has been extended by Furchgott and co-workers27,46 and others77-79 to demonstrate a critical role of the endothelium in mediating vasodilation in response to a variety of stimuli. It has also been suggested that increases in blood flow velocity may play a significant role in mediating vasodilation.50,52 Very likely through an endothelium-dependent mechanism.22,53,54 While the physiological significance of these indirect mechanisms has not been clearly defined, it is obvious from recent studies that removal of endothelium alters normal vascular function. The factors mediating vasodilation are thus a combination of endothelium-dependent, blood-flow-dependent, and direct actions of agents on the vascular smooth muscle. The following discussion includes the more widely studied mechanisms of vasodilation.

1. Endothelium-dependent Vasodilation. The recent discovery by Furchgott and co-workers27,46 that an intact vascular endothelium is required to elicit vasodilation to acetylcholine has led to an intense investigation of endothelium-mediated vasodilation. While the precise mechanism by which the endothelium mediates smooth muscle relaxation is not well understood, and its physiologic and pathologic significance is unknown, it is clear that the vascular response to many compounds is altered in the absence of intact endothelium. Furchgott has recently reviewed the extensive literature regarding the endothelium and vascular smooth muscle,46 indicating that regulation of vascular smooth muscle by the endothelium is complicated by species differences and also by regional tissue differences. There are relatively few studies that have addressed the role of endothelium in intact vascular beds. Nevertheless, it is well recognized that the relaxation of isolated arteries to acetylcholine,27,55 ATP and ADP,56 serotonin,48 arachidonic acid,57 bradykinin,55 and thrombin38 is mediated either partially or entirely by the release of a factor(s) from the endothelial cells. In contrast to these observations, an intriguing preliminary report in conscious dogs suggests that smooth muscle cells assume an endothelial-type function if the endothelium is removed from coronary arteries.59 In that study, despite removal of endothelium by a balloon catheter, a normal vasodilator response to acetylcholine reappeared after three days. One consideration for studies inducing de-endothelialization by balloon catheters is the potential for disruption of the media as well as the endothelium.

One mechanism accounting for endothelium-mediated relaxation of the coronary artery involves endothelial cell production of prostacyclin. Inhibition of prostacyclin synthesis with indomethacin has recently been shown to increase basal tone and potentiate the contractions to prostaglandin F2α in isolated coronary arteries60,61 and decrease baseline coronary artery diameter in conscious dogs.62 However, smooth muscle production of prostacyclin probably mediates some of the relaxant response to arachidonic acid since the relaxation also persists following removal of the endothelium.57,63 Inhibitors of lipoxygenase did not affect the relaxation of isolated coronary arteries to arachidonic acid.63

A second vasorelaxant compound produced by the endothelial cells is the "endothelium-derived relaxant factor" (EDRF) described by Furchgott.46 Existing evidence mitigates against prostaglandins as the putative EDRF since cyclooxygenase inhibition does not affect endothelium-mediated relaxation and suggests instead that EDRF is a lipoxygenase metabolite of arachidonic acid or other unsaturated fatty acid released by activation of phospholipase. This hypothesis is based on data that report inhibition of endothelium-dependent relaxation by quinacrine (an inhibitor of phospholipase A2), and nordihydroguaiaretic acid and 5,8,11,14-eicosatetraynoic acid (both inhibitors of lipoxygenases). The evidence leading to this scheme has been critically reviewed by Furchgott46 and is beyond the scope of this paper. However, since there are profound tissue differences, and much of the work has been conducted in vessels other than coronary arteries, application of some of the previous work to coronary vascular control may be limited.

2. Blood-flow-mediated Vasodilation. Changes in blood flow through large arteries, in the absence of pharmacological stimuli, produce proportionate changes in vessel diameter. Although the precise
mechanism by which these changes occur is not clear, it has been postulated that endothelial cells function as "sensors" of changes in blood flow or shear stress, regulating vessel caliper through release of EDRF. Control of vascular caliper by changes in blood flow was first postulated in 1933 by Schretzenmayr who observed dilation of the in situ canine femoral artery in response to elevations in femoral artery blood flow. Originally, the mechanism of this vasodilation was believed to be a wave of vasodilation propagated from the arterioles, retrograde into the larger proximal arteries. This phenomenon was termed "ascending dilation." Other experiments, in which the femoral artery was cut distal to an AV fistula, however, ruled out the possibility of a propagated wave of vasodilation. This was first verified in the coronary circulation by Gerova et al who isolated and perfused in situ a segment of the left anterior descending (LAD) coronary artery. Following an approximate 10-fold increase in blood flow through the segment, the diameter of the vessel increased by 3.6% of its resting diameter. These authors concluded that such an increase in epicardial coronary diameter may counteract the tendency toward vasoconstriction produced during potent sympathetic neural stimulation. More recently, work by Segal and Duling has revived the interest in the ascending dilation theory, and has demonstrated that the microcirculation of hamster vessels (<50 μm) may propagate a wave of dilation independent of changes in blood flow.

The observation of blood-flow-mediated changes in coronary caliper have been extended to conscious dogs. Hintze and Vatner and Holtz et al have demonstrated that the release of a transient coronary occlusion produced an increase in coronary diameter that was abolished if flow was restricted to preocclusion baseline levels (Figure 1). Hintze and Vatner termed the phenomenon "reactive dilation" to signify

![Graph](https://example.com/graph.png)

**Figure 1.** An example of the reactive hyperemia and reactive dilation following release of a 10-second coronary artery occlusion in a conscious dog. In the left panel, coronary blood flow was unrestricted, while in the right panel coronary blood flow was prevented from rising by partial inflation of an hydraulic occluder implanted distal to the dimension transducers. The dilation of the large artery is mediated by an increase in blood flow since it is abolished when coronary blood flow is restricted upon release of the occlusion.
the response of the large artery during the concomitant small vessel reactive hyperemia. Similar flow-dependent dilation has been demonstrated in response to intracoronary papaverine and intravenous adenosine and dipyridamole, while the effects of acetylcholine and the calcium antagonists nifedipine, diltiazem, and verapamil appear to be only partially due to increases in blood flow. Flow-dependent dilation may also occur in vessels smaller than 50 µm.

Although the flow-mediated changes in coronary caliper have been attributed to endothelial cells and the release of EDRF, no study of the intact coronary circulation has verified the participation of endothelial cells. A recent report by Pohl et al. using isolated perfused segments of canine femoral arteries demonstrated good correlation between perfusion rate and segment diameter, which was abolished in segments removed of endothelium. While it is reasonable to assume that the endothelium participates in the flow-mediated dilation, a direct involvement in coronary vessels remains to be demonstrated. Recently, two laboratories have presented preliminary reports concluding that removal of endothelium abolishes flow-dependent coronary dilation in response to adenosine and release of transient coronary artery occlusion.

The mechanism of the flow-induced changes in coronary caliber is unknown. It is unlikely that changes in intraluminal blood pressure are responsible. Vascular endothelial cells are subject to structural and functional changes during changes in blood-flow patterns, and may respond to changes in blood flow with the release of vasoactive metabolites. It is possible that these factors are identical or similar to the EDRF released by acetylcholine. In this regard, a preliminary report has demonstrated that methylene blue, an inhibitor of soluble guanylate cyclase and an inhibitor of nitrolycerin-induced vasodilation, reduces the flow-dependent dilation of in situ canine femoral arteries.

3. Dilation mediated by beta-adrenoceptors. Prior studies of the coronary circulation in vivo have demonstrated that dilation mediated by beta-adrenoceptors is predominantly controlled by the beta-2-adrenoceptor subtype. These studies have been reviewed previously and, as pointed out by Feigl, usually discuss vasodilation in terms of coronary blood flow or resistance of small coronary vessels. In contrast to these studies, work in isolated large coronary arteries have almost exclusively demonstrated that beta-adrenoceptors in the large vessels are of the beta-1 subtype. For example, Baron et al. compared the response of coronary and femoral vessels to beta-activation by isoproterenol, nor-epinephrine, and epinephrine. Beta-Activation of the coronary arteries produced relaxation that was significantly attenuated by concentrations of practolol, which did not affect relaxation in the femoral vessels. The authors concluded that beta-1 adrenoceptors predominate in large coronary vessels, while beta-2 receptors are more important in arteries of skeletal muscle. Similar studies using beta-specific antagonists have demonstrated primary control by beta-1 adrenoceptors in isolated coronary vessels of swine, rabbits, and kittens. In addition, the relatively low potency of the beta-specific agonist salbutamol, in relaxing isolated coronary arteries has been taken as evidence that coronary beta-2 adrenoceptors are unimportant in mediating vasorelaxation. Only one study, which was conducted in pigs, has reported a predominant action of beta-2 adrenoceptors in the coronary arteries.

Relatively few studies have examined the responses of large coronary arteries in vivo to beta-adrenoceptor activation. Clinical studies have suggested that beta-blockade with propranolol may exacerbate episodes of angina pectoris and coronary vasoconstriction. A previous study from our laboratory evaluated the role of beta-adrenoceptors in mediating large coronary artery vasodilation in intact, conscious animals and found that selective activation of either beta-1 or beta-2 receptors produced significant increases in large coronary artery cross-sectional area, indicating that both beta-1 and beta-2 activation can elicit substantial vasodilation. However, it is uncertain from those experiments whether beta-activation produced direct vasodilation or dilation mediated via metabolic or flow-mediated mechanisms. One possibility is that beta-adrenoceptor stimulation dilates large coronary arteries via a blood-flow--dependent mechanism associated with a rise in metabolic demand and coronary blood flow. Vatner and Hintze also demonstrated significant reduction in large coronary diameter following beta-blockade with either propranolol or atenolol and concluded that the constriction was primarily due to a lower metabolic demand. The reduced metabolic demand would be expected to decrease large coronary caliber due to a decrease in blood-flow mediated dilation and reduced production of adenosine or other metabolically released metabolites. Recent studies from our laboratory indicate that beta-adrenergic vasodilation in the large coronary artery can occur independently from increases in coronary blood flow. In those studies, isoproterenol, which stimulates beta-1 and beta-2 adrenoceptors, and propranolol and pirbuterol, which stimulate primarily beta-2 receptors, respectively, were administered intracoronary to conscious, chronically instrumented calves. All three agents elicited marked large coronary artery vasodilation, which was unaffected by holding coronary blood flow constant (Figure 2). Using ligand-binding techniques to assess beta-adrenoceptors in bovine and porcine coronary artery membrane preparations, both types of beta-adrenoceptor subtypes were identified in large coronary arteries, with a predominance of the beta-1 receptor subtype. It has also recently been proposed that beta-adrenergic vasodilation in canine coronary artery in vitro, canine iliac artery in vivo, and rat femoral arteries may be partially endothelium dependent. Other studies suggested that beta-blockade elicits direct coronary constriction by unmasking the effect of postjunctional alpha-adrenoceptors, increasing Ca^2+ permeability or decreasing Na^+ / K^+ -ATPase activity. However, in the study by Vatner and Hintze, beta-adrenoceptor block-
FIGURE 2. An example of β-adrenergic dilation with isoproterenol (ISO 0.0025 μg/kg, administered via an indwelling catheter at the origin of the left circumflex coronary artery) of the large coronary artery in a conscious calf. The dilation was only slightly reduced when blood flow was limited to control levels by partial inflation of a distal hydraulic occluder, indicating that isoproterenol has a direct effect on the large coronary artery. Reproduced with permission from Valner et al: Circ Res 1986;59:463-473.

...induced even greater vasoconstriction in the presence of α-adrenoceptor blockade, making the mechanism of unmasked α-adrenergic tone unlikely. The involvement of other mechanisms (endothelium, blood flow, metabolic demand, etc.) in the control of large arteries by β-adrenoceptor stimulation or blockade remains to be clarified.

It should be pointed out that in addition to dilation mediated by β-adrenoceptors, recent studies have suggested that α2-adrenoceptors located on endothelial cells may mediate vasodilation via release of an endothelial relaxant factor. This is based on the observation that removal of the endothelium abolished α2-mediated relaxation or potentiated α2-mediated contraction in isolated vessels. α2-Mediated endothelium-dependent relaxations have not been demonstrated in vivo. In fact, recent work in our laboratory demonstrated only contraction of the iliac artery with BHT 920, which is not affected by removal of the endothelium.

4. CHOLINERGIC REGULATION. As noted above, a long-standing controversy has existed regarding cholinergic or parasympathetic control of the coronary circulation. Studies using isolated segments of large coronary arteries have mainly demonstrated that acetylcholine induces contraction. In contrast, in the intact canine circulation acetylcholine produces vasodilation and increases in coronary blood flow. These results are not necessarily contradictory since changes in coronary blood flow reflect changes in resistance vessels, while isolated vascular studies usually employ larger epicardial arteries. It is possible that large and small vessels respond differently to acetylcholine administration. The consistent demonstration...
that acetylcholine contracts isolated coronary arteries led to the hypothesis that acetylcholine or parasympathetic neural activity could be a major factor in the etiology of vasospasm. In support of this concept, clinical studies have demonstrated provocation of large coronary artery vasospasm by subcutaneous injection of the muscarinic agonist methacholine.\textsuperscript{106,109} Subsequent studies apparently yielded an explanation for this observation, when Furchgott and Zawadzki\textsuperscript{27} described the requirement for an intact endothelial cell layer to elicit cholinergic vasorelaxation and suggested that cholinergically mediated spasm occurred at damaged portions of the large coronary artery.

An alternative to that of endothelial damage as an explanation of cholinergic vasoconstriction must be considered. Evidence is accumulating to indicate that species differences may account for some of the disparity regarding the coronary vascular response to cholinergic agonists. In the canine circulation, both large and small coronary vessels respond to acetylcholine with vasodilation, provided the endothelium is intact.\textsuperscript{45,108-112} Other studies have recently demonstrated that the coronary circulation of baboons and rhesus monkeys responds to cholinergic stimulation solely with dose-dependent vasoconstriction,\textsuperscript{111,113} although these studies did not examine the response of large coronary arteries. Similar findings have been reported in the coronary resistance vessels,\textsuperscript{111} and isolated large coronary arteries of pigs, cats, and rabbits.\textsuperscript{41,42,86} Recent work in our laboratory also indicates that acetylcholine can elicit a phase of potent vasoconstriction in the baboon but only induces coronary vasodilation in the dog. In view of the studies reporting cholinergic vasoconstriction in both large and small coronary vessels, in which the endothelium is most likely intact, it cannot be arbitrarily assumed that a contractile response to cholinergic stimulation is due to a damaged endothelium. In this regard, Ginsburg et al\textsuperscript{29} reported that isolated human coronary arteries contract with administration of the muscarinic agonist carbachol, despite the presence of an intact endothelium. Ludmer et al\textsuperscript{44} have also recently demonstrated that intracoronary injection of acetylcholine results in coronary vasoconstriction in humans with coronary artery disease.

While it is well accepted that acetylcholine has profound effects on large and small coronary arteries, the effects of parasympathetic nerve stimulation are not clear. Several studies have demonstrated the presence of parasympathetic nerve endings in the adventitia of the large and small coronary vessels.\textsuperscript{115,116} Reid et al\textsuperscript{117} have recently demonstrated that stimulation of the cervical vagus nerves elicits vasodilation of small coronary vessels and increases coronary blood flow. Similar findings have not been reported for the control of large coronary arteries. In fact, Gerova et al\textsuperscript{118} were unable to elicit dilation of epicardial coronary arteries with direct vagal stimulation. These authors\textsuperscript{118} suggested that 1) the parasympathetic fibers simply ran parallel to the large artery without innervating smooth muscle cells, and 2) the nerve terminals may serve only to modulate the release of adrenergic transmitter, as later discussed by Vanhoutte et al.\textsuperscript{119} Others have demonstrated that the most extensive parasympathetic innervation of the ventricles surrounds the ventricular conduction system\textsuperscript{120} and probably enters and distributes throughout the ventricle via subendocardial pathways.\textsuperscript{121} This pattern of innervation may account for the relative lack of parasympathetic innervation of epicardial coronary vessels. Thus, the extent of cholinergic regulation of large coronary arteries remains controversial, particularly the importance of neurally mediated effects and of the roles of the endothelium and species differences.

5. Purinergic regulation. The purine nucleotides and nucleosides, specifically adenosine triphosphate (ATP) and adenosine, have received considerable attention as possible physiologic local regulators of coronary vasoactivity.\textsuperscript{14,122,123} While ATP and adenosine diphosphate (ADP) are more potent than adenosine in relaxing isolated vascular smooth muscle,\textsuperscript{36,124} the role of the adenosine nucleotides in control of coronary vasoactivity is probably relatively small due to their rapid degradation to adenosine.\textsuperscript{14} Dipyridamole and lidoflazine, compounds that prevent cellular uptake and metabolism of adenosine, are also potent coronary vasodilators.\textsuperscript{125}

Adenosine is believed to be one of many important regulators of coronary blood flow in response to increased cardiac performance, occlusive ischemia, and hypoxia,\textsuperscript{14} yet few studies have examined its role in regulation of large coronary vessels. While several have shown that adenosine also dilates isolated large coronary arteries,\textsuperscript{45,108,127} several other studies suggest it is more effective in relaxing small coronary vessels. Schnaar and Sparks\textsuperscript{3} compared relaxation of large (\(>1\) mm) and small (\(<0.5\) mm) isolated coronary arteries to nitroglycerin and adenosine. Nitroglycerin caused greater relaxation of large vessel segments while the converse was true for adenosine. Harder et al\textsuperscript{8} extended this finding to show that calcium-dependent action potentials in large coronary segments were unaffected by adenosine but were abolished in small coronary vessels. In contrast, nitroglycerin abolished the action potentials in segments of large coronary artery but not in small arteries.\textsuperscript{8} These studies in isolated vessels agree with earlier reports in the intact coronary circulation, which suggested that adenosine and dipyridamole did not decrease large coronary artery resistance and, in fact, caused small increases in resistance.\textsuperscript{1,2,128}

More recently, the direct ultrasonic measurement of large coronary artery diameter in conscious dogs has yielded different results regarding adenosine's action on large coronary vessels. Hintze and Vatner\textsuperscript{33,129} observed a 30% increase in large coronary artery cross-sectional area following intravenous administration of either adenosine or dipyridamole. These increases were significantly attenuated by pretreatment with the adenosine receptor antagonist aminophylline. In contrast, release of a 15-second circumflex coronary artery occlusion elicited a "reactive dilation," which was not attenuated significantly by aminophylline. Further-
more, preventing reactive hyperemia following a brief period of coronary artery occlusion abolished the "reactive dilation." Yet preventing adenosine-induced hyperemia only partially reduced the dilation of the large artery during adenosine injection. The study by Hintze and Vatner\textsuperscript{73} differs slightly from the results of Holtz et al\textsuperscript{22} who found that flow restriction completely offset the large coronary dilation with adenosine. However, the control dilations observed by Holtz et al\textsuperscript{22} were approximately half those reported by Hintze and Vatner,\textsuperscript{73} suggesting that the vessels were not as reactive. Thus, the effects of adenosine and dipyridamole are partially due to an increase in coronary blood flow, which exerts an indirect effect on large artery caliber, but these compounds most likely have an additional direct action on the coronary smooth muscle cells. In this regard, previous studies in the canine femoral artery suggest that ATP, but not adenosine, exerts\textsuperscript{56} an effect indirectly via the endothelium.\textsuperscript{56} However, a recent report using isolated coronary artery segments has suggested that adenosine-induced relaxation is partially endothelium dependent.\textsuperscript{56}

Adenosine may also dilate epicardial coronary arteries by its action on the adventitial surface of the vessels. Studies have suggested that adenosine formed in the myocardium may be released into the pericardial fluid and that pericardial fluid levels of adenosine may be used as an index of myocardial adenosine production.\textsuperscript{130,131} Although the contribution of pericardial adenosine levels to dilation of large coronary arteries has not been studied directly, it is likely that adenosine in pericardial fluid has some vasoactive effects. A similar mechanism for coronary dilation has been proposed for prostacyclin released from the pericardium.\textsuperscript{122}

One common mechanism of action for cholinergic and purinergic compounds deserves mention. In the coronary circulation, which is densely innervated with both adrenergic and cholinergic neurons, the release of norepinephrine from the sympathetic post-ganglionic fibers is inhibited by prejunctional action of acetylcholine\textsuperscript{119} and adenosine.\textsuperscript{133} The physiological significance of this negative feedback system is unknown, but it is tempting to speculate that acetylcholine or adenosine, in addition to their direct vascular actions, may also regulate sympathetic tone of the large coronary arteries.

6. DIRECT VASODILATION. In contrast to indirect vasodilation produced by elevation of coronary blood flow or mediated by the endothelium, direct coronary vasodilation can result from a membrane or intracellular event not mediated by a specifically characterized receptor. Examples of these types of mechanisms are the nitrate vasodilators, papaverine, and the calcium channel blockers. While the ability of these compounds to increase coronary blood flow is well known, their primary action in the treatment of coronary artery disease in general and coronary vasospasm in particular most likely involves their action on the large epicardial and collateral coronary vessels. This action was first described for nitroglycerin by Fam and McGregor,\textsuperscript{4} who demonstrated in chronically ischemic dogs with a well-developed collateral circulation that nitroglycerin caused a significant increase in retrograde collateral blood flow without an increase in total coronary flow. In contrast, that study reported no increase in retrograde flow following dipyridamole, despite an increase in total coronary flow. These authors postulated that nitroglycerin acted primarily on large conductance and collateral vessels, while dipyridamole dilated mainly small vessels. This was later confirmed in studies by Fam and McGregor\textsuperscript{4} and Winbury et al\textsuperscript{12} who compared these two compounds in anesthetized, open-chest dogs. The therapeutic action of nitroglycerin in relieving vasospasm and angina pectoris was thus attributed to a redistribution of blood flow to the ischemic myocardium.

In contrast, studies on the effects of calcium channel blockers (prenylamine, perhexiline, verapamil, nifedipine) reported that these compounds did not decrease large coronary artery resistance, and in fact, caused small increases in large coronary artery resistance.\textsuperscript{2,134} This is surprising in view of the large number of studies demonstrating relaxation of isolated epicardial coronary arteries by calcium channel blockers.\textsuperscript{135-137} More recent studies in intact, conscious animals\textsuperscript{138,139} and man\textsuperscript{140} demonstrated that the calcium channel blocker nifedipine does indeed dilate large epicardial coronary vessels. The relative lack of effect of the calcium channel blockers in anesthetized animals is probably due to a diminished level of smooth muscle tone resulting from a combination of general anesthesia and the concomitant tachycardia.\textsuperscript{52,67,141,142} These effects would not be evident in chronically instrumented animals or in studies that utilize noninvasive diameter measurements.

It is not unexpected that calcium channel blockers should increase coronary diameter, since their primary mode of action is blockade of extracellular calcium influx.\textsuperscript{143} In this regard, both canine\textsuperscript{58} and human\textsuperscript{59} coronary arteries utilize extracellular calcium sources for contraction of smooth muscle. The mechanism by which nitroglycerin relaxes vascular smooth muscle is less well understood, though a recent report has demonstrated that both calcium channel blockers and nitroglycerin can abolish calcium-dependent action potentials in large coronary arteries.\textsuperscript{8} Nitroglycerin also elevates smooth muscle cell levels of cyclic guanosine monophosphate (GMP) in proportion to the magnitude and the time course of relaxation.\textsuperscript{80,144} Since calcium blockers more effectively inhibit contractions dependent on extracellular calcium, and the nitrate vasodilators selectively inhibit those dependent on intracellular calcium, it is likely that these direct vasodilators operate via different mechanisms to decrease coronary vascular tone.\textsuperscript{145} It should be emphasized that these studies of calcium flux have been conducted primarily on large coronary arteries, and the results may not be indicative of calcium regulation and vascular contraction in small vessels.

7. PROSTAGLANDINS AND ARACHIDONIC ACID METABOLITES. The pharmacology, synthesis, and ac-
tions of the many prostanoid compounds have been comprehensively reviewed elsewhere,\textsuperscript{146,147} yet there is no consensus regarding the role of prostaglandins in the physiological or pathological control of large coronary artery vasoactivity.

Arachidonic acid is the precursor of the biologically important prostaglandins (PG), PGE\textsubscript{2}, PGI\textsubscript{2}, prostacyclin, and thromboxane A\textsubscript{2}, all metabolites of the cyclooxygenase pathway. In addition, arachidonic acid can be metabolized by lipooxygenase enzymes to form derivatives of eicosatetraenoic acid and the leukotrienes. The cardiovascular actions of these lipooxygenase products are uncertain, but they may be involved in endothelial-mediated vasodilation,\textsuperscript{46} leukocyte chemotaxis,\textsuperscript{146,148} and inhibition of prostacyclin synthesis.\textsuperscript{146} Because the metabolism of arachidonic acid or the biosynthesis of prostaglandins varies with different tissues and species, the action of prostaglandins on vascular smooth muscle is the integrated result of the relative vasoconstrictor and vasodilator components. The relaxation of coronary vessels in response to arachidonic acid is due to the synthesis of prostacyclin. It has been demonstrated that prostacyclin is the major metabolite of arachidonic acid in blood vessels,\textsuperscript{146,148} and its synthesis is greatest at the intimal surface and endothelium.\textsuperscript{149} There may also be regional coronary differences in the metabolism of arachidonic acid and production of prostaglandins. A report by Gerritsen and Printz\textsuperscript{150} demonstrated that microsomes from bovine epicardial coronary arteries converted arachidonic acid primarily to prostacyclin, while microsomes of small vessels (<100 \mu m) produced PGE\textsubscript{2}. No thromboxane synthesis by coronary microsomes was observed in response to arachidonic acid. Whether similar regional differences exist in the vasomotor response of large and small vessels to various prostaglandins remains to be demonstrated.

Despite the recognition that prostacyclin is a vasodilator of both large and small coronary arteries, a physiological role for the prostaglandins has not been adequately demonstrated. Prostacyclin is released by the coronary vessels in response to arterial hypoxia, transient coronary occlusion, bradykinin, and angiotensin II, but inhibition of cyclooxygenase was reported to have only small effects on the response of coronary blood flow to these interventions.\textsuperscript{132,151} In isolated large coronary vessels, cyclooxygenase inhibition universally increases resting tension,\textsuperscript{60,152,153} but the significance of this observation is uncertain. Few studies have examined the effects of prostacyclin and cyclooxygenase inhibition on large coronary artery caliber \textit{in situ}. Dusting and Angus,\textsuperscript{19} using a segment of canine coronary artery isolated and perfused \textit{in situ}, demonstrated that prostacyclin produced only small increases in epicardial coronary artery diameter, at concentrations which profoundly reduced arterial pressure. They also reported that indomethacin did not change resting coronary diameter and suggested that prostacyclin was a relatively weak dilator of large coronary vessels compared to the small resistance vessels. This concept is supported by recent work examining coronary dilation with prostacyclin in conscious dogs.\textsuperscript{20,26} Another study by Holtz et al\textsuperscript{62} investigated the role of prostaglandins in the blood flow-dependent, endothelial-mediated dilation of epicardial arteries in conscious dogs. In that study, cyclooxygenase inhibition reduced resting coronary diameter, yet did not alter the dilation of the large coronary arteries in response to elevated coronary blood flow.

The regulation of coronary vascular tone by cyclooxygenase products may vary in diseased coronary vessels. In humans with coronary artery disease, cyclooxygenase inhibition with indomethacin reduced coronary sinus blood flow and increased coronary vascular resistance, despite an increase in myocardial oxygen consumption.\textsuperscript{154} In intact, closed-chest dogs, cyclooxygenase inhibition resulted in significant focal vasoconstriction of de-endothelialized coronary arteries, while intact arteries were unaffected.\textsuperscript{155} These studies suggest that smooth muscle production of vasodilator prostaglandins may promote a tonic level of protection against vasoconstriction in diseased vessels or in vessels with damaged endothelium.

In addition to its potent vasodilator action, prostacyclin possesses powerful activity against platelet aggregation.\textsuperscript{146,148} Since platelets are the primary source of the vasoconstrictor compound thromboxane A\textsubscript{2}, which promotes platelet aggregation, it has been proposed that the vascular actions of arachidonate metabolism represent a balance of vasodilator and vasoconstrictor actions, which is critically dependent upon the degree of platelet aggregation and activation.\textsuperscript{19,147} The high vascular production of prostacyclin in normal vessels likely minimizes platelet aggregation. However, reduced prostacyclin synthesis in damaged or atherosclerotic vessels would favor platelet aggregation, thrombus formation, vasoconstriction, and vasospasm.\textsuperscript{148,156} While there is little direct evidence that thromboxane A\textsubscript{2} constricts large coronary vessels \textit{in vivo}, its stable analog (U 46619) is a potent vasoconstrictor of large coronary arteries.\textsuperscript{19} Thromboxane A\textsubscript{2} has been implicated in the pathogenesis of vasospasm.\textsuperscript{157,158} However, recent studies have indicated that reduction of thromboxane A\textsubscript{2} levels with aspirin\textsuperscript{159} or elevation of prostacyclin levels by exogenous infusion\textsuperscript{159} did not reduce incidence of attacks in patients with vasospastic angina.

\section*{II. Mechanisms of Coronary Vasoconstriction}

In contrast to the numerous studies examining the role of pharmacologic vasodilation in large arteries, relatively few studies have investigated \textit{in vivo} the regional response of the coronary circulation to vasoconstrictor stimuli.

1. \textbf{Vasoconstriction mediated by \textalpha{}-adrenoceptors.} The epicardial coronary vessels are densely innervated with sympathetic adrenergic nerve fibers.\textsuperscript{12,28} The adrenergic nerves seen in the adventitia of epicardial coronary arteries probably represent both terminal varicosities as well as nerves running along the vessel to innervate smaller vessels and the myocardium. Thus, it is not directly possible to deter-
mine the exact extent to which large coronary arteries are innervated.

In isolated vessel preparations, the responses of large coronary arteries to catecholamines have been shown by Zuberbühler and Bohr to favor adrenergic vasoconstriction, while the smaller vessels respond with relaxation. This difference in the sensitivity of large and small vessels has led to the suggestion that the epicardial vessels, in the absence of the metabolic influences that control the small vessels, may be a primary site for control of coronary blood flow by adrenergic mechanisms. Kelley and Feigl, using a constant pressure-perfused coronary preparation in open-chest dogs, measured large and small artery resistance changes during bolus injections of norepinephrine and during stellate ganglion stimulation. In the presence of β-adrenergic receptor blockade, α-receptor activation with norepinephrine and stellate stimulation elevated large coronary artery resistance by 28% and 12%, respectively, above baseline levels, which are less than that observed in the distal coronary vessels. These authors concluded that the epicardial coronary arteries are not the dominant site of sympathetic coronary vasoconstriction.

Malindzak et al observed larger changes in proximal coronary resistance (approximately 100%) in anesthetized dogs. The experimental preparation that was used limits comparison with the results from the study of Kelley and Feigl, but from both studies it is clear that the coronary vessels contribute less than 10% of the total coronary resistance even under conditions of elevated sympathetic tone. Gerova et al studied the constriction of a large coronary artery to electrical stimulation of the stellate and thoracic ganglia in anesthetized dogs. Per fused at constant pressure, the large artery constricted during stellate stimulation by 4% of the external diameter. Based on the change in radius, this change in epicardial coronary resistance is similar to that reported by Kelley and Feigl. A recent study by Vatner et al demonstrated in conscious dogs instrumented to measure circumflex coronary diameter ultrasonically that methoxamine, a selective α,adrenoceptor agonist, produced a 27% decrease in cross-sectional area despite a 65% rise in arterial pressure (Figure 3). Similar results have been obtained by Bassenge et al with vasopressin, angiotensin, and stellate ganglion stimulation. Thus, large coronary arteries have the ability to constrict with neural stimulation or circulating α-adrenoceptor agonists. However, the similarity of resistance changes in large and small vessels observed during α-adrenoceptor activation indicate that while the large vessels participate in changes in coronary vascular resistance, they are not the primary source of these changes. Furthermore, Chierchia et al suggested that α-adrenoceptor stimulation was not the primary mechanism of vasospasm in humans, citing the failure of phentolamine to reduce episodes of angina and the inability of phenoxyphrine, norepinephrine, or cold pressor test to provoke spasm in patients testing positive with ergonovine.

Several recent studies in canine large coronary arter-
The mechanism of constriction by the ergot alkaloids is complex. In canine femoral veins,\textsuperscript{179} rat aorta, and dog femoral artery\textsuperscript{180} and rabbit carotid and femoral arteries,\textsuperscript{173} ergonovine contractions are mediated by $\alpha$-receptors. In canine\textsuperscript{170,171} and rabbit\textsuperscript{173} coronary arteries, the response to ergonovine is unaffected by $\alpha$-adrenoceptor blockade, but inhibited by the serotonin receptor antagonist, methysergide. In humans, ergonovine-induced coronary vasospasm has been reversed by $\alpha$-adrenoceptor blockade with phentolamine\textsuperscript{181} and is thus believed to consist of a significant $\alpha$-adrenergic component.\textsuperscript{168,182} The existence of $\alpha$-adrenoceptor activation in addition to stimulation with serotonin may partially explain ergonovine's spasmogenic action in humans, whereas it is ineffective in eliciting spasms in experimental animals.

In contrast to the action of ergonovine, it is believed that serotonin produces coronary vasoconstriction by stimulating exclusively serotonin receptors. However, in some tissues serotonin stimulates $\alpha_1$-adrenoceptors.\textsuperscript{173,183} Coronary vasoconstriction with serotonin in isolated vessel segments is blocked by the nonspecific serotonin antagonist methysergide and the specific serotonin (5-HT$_2$) receptor antagonist ketanserin at

![Diagram](http://cirche劳动者.ahajournals.org/ Downloaded from)

**Figure 3.** The effects of a 10-minute infusion of methoxamine, 50 $\mu$g/kg/min, in a conscious dog are depicted on simultaneous and continuous measurements of phasic and mean left circumflex coronary artery diameter, aortic root pressure, left ventricular pressure, left ventricular dP/dt, and phasic and mean left circumflex coronary blood flow. Methoxamine increased coronary diameters only initially and transiently and then induced striking sustained reductions in coronary diameters at a markedly elevated aortic pressure. At the end of the response, the vessel was transiently occluded to obtain a zero blood flow reference. Reproduced with permission from Vatner et al: J Clin Invest 1980;65:5-14.
concentrations that are largely ineffective against α-agonists. Conversely, the contraction of canine coronary arteries by serotonin is not affected by doses of prazosin, which significantly inhibit phenylephrine-induced contraction.

Serotonin administered to the intact coronary circulation elicits only vasoconstriction of the large coronary arteries. In isolated coronary segments without resting tone, serotonin also elicits contraction. The contraction elicited by serotonin in both intact and isolated coronary arteries is enhanced in vessels without an intact endothelium. In isolated vessels that are preconstricted to achieve resting tone, serotonin produces relaxation provided the endothelial cell layer is intact, while in the absence of endothelial cells serotonin further contracts preconstricted vessels. The contraction of intact vessels is blocked by the selective antagonist ketanserin, while the endothelium-dependent relaxation is blocked by methysergide and methiothepin, but not ketanserin. One piece of evidence against the concept of direct stimulation by serotonin on smooth muscle is the observation that methiothepin, but not ketanserin, inhibited contraction in de-endothelialized arteries. The reason for this discrepancy is not clear. While the distinction between 5-HT and 5-HT receptors was originally described in brain tissue, a similar distinction in vascular tissue has not been demonstrated. It is therefore important to point out that the actions of methiothepin on vascular responses to serotonin may not signify a specific action on the 5-HT receptor subtype. Thus, serotonin has two opposing mechanisms of action: 1) direct vasoconstriction mediated by 5-HT receptors on smooth muscle cells and 2) indirect endothelium-dependent vasodilation mediated via receptors other than the 5-HT subtype on the endothelial cells. The predominance of vasoconstriction in the intact circulation and its enhancement following removal of endothelium suggest that the 5-HT-mediated dilation is weak, but sufficient to counteract a portion of the vasoconstriction. The location and possible involvement of 5-HT-receptor subtypes in the vascular action of serotonin awaits further clarification.

Aggregated platelets have an action on isolated coronary vessels similar to that of serotonin. Platelet suspensions contract quiescent vessel segments, but relax segments precontracted with prostaglandin F2 or norepinephrine. In the absence of endothelium, the contraction of quiescent segments is enhanced, and precontracted vessels respond with further contraction. The results of recent work suggest that the relaxation produced by platelets in vessels with intact endothelium is in part due to serotonin, but primarily to the endothelium-dependent effects of ADP and ATP released from the platelets. The contraction of quiescent or de-endothelialized vessels is probably a result of released serotonin. However, aggregated or activated platelets also release thromboxane A2, a metabolite of cyclooxygenase and a potent constrictor of vascular smooth muscle. The vasoconstrictor actions of thromboxane A2 along with the observation that thromboxane B2 (the stable metabolite of thromboxane A2) levels are elevated in patients with coronary disease has fostered speculation that thromboxane A2 released from platelets may be involved in episodes of coronary constriction or vasospasm. While the actions of thromboxane A2 appear to be unaltered by the endothelium, a disrupted endothelial cell layer may promote vasoconstriction due to thromboxane A2, especially if endothelial cell production of prostacyclin is diminished, as it is in atherosclerotic arteries. These actions suggest a possible physiologic and pathologic role of aggregated platelets, which may dilate normal vessels, but constrict a vessel with pre-existing endothelial damage, potentially eliciting vasospasm.

Another result of platelet aggregation is the phenomenon of cyclic reductions in coronary blood flow described by Folts et al. These authors demonstrated that spontaneous platelet aggregates at a pre-existing coronary stenosis occlude the large coronary artery sufficiently to reduce coronary blood flow, resulting in ischemia, dysrhythmias, and death. The platelet aggregation and flow reductions are abolished by inhibition of cyclooxygenase, thromboxane synthetase, and blockade of 5-HT or α-adrenoceptors, suggesting that factors released from platelets are involved. It is not clear at this time whether active constriction of the coronary artery also occurs during the development of occlusive thrombi, or whether this is a purely passive phenomenon. Nonetheless, platelet aggregation at sites of stenosis may represent a major cause of myocardial ischemia and infarction.

3. CHOLESTEROL AND ATHEROSCLEROSIS. Coronary vasospasm in humans can occur in angiographically normal arteries. However, in patients with sites of coronary artery stenosis, spontaneous or provoked spasm occurs primarily as constriction superimposed on the stenosis. This observation, along with the fact that ergonovine-induced spasm occurs at the same site as spontaneous spasm, have led to the hypothesis that coronary spasm results from vascular smooth muscle hyperactivity associated with vascular injury or damage. Support for this idea is found in a number of recent studies reporting augmented vasoconstriction in isolated vessels or in situ vascular beds acutely or chronically exposed to elevated levels of cholesterol. Isolated canine coronary arteries contract when exposed to low concentrations of cholesterol. Furthermore, the presence of cholesterol in the bathing medium significantly enhances the coronary constriction effects of potassium and calcium ions. A more recent report demonstrated the sensitization of the intact coronary resistance vessels to both adrenergic dilation and constriction in dogs fed cholesterol-rich diets for one month. These authors suggested that an alteration in metabolism, binding, or uptake of catecholamines was responsible for the sensitization, in contrast to Yokoyama and Henry who advocated an altered membrane environment and increased calcium permeability. One other report has demonstrated an enhanced sensitivity to norepinephrine in the hindlimb
resistance vessels in monkeys fed cholesterol-rich diets for 4-5 months. This study failed to demonstrate effects of high cholesterol on reactivity of large hindlimb vessels, and while potentially not directly applicable to the coronary vessels, suggested that cholesterol may affect large and small vessels differently. The duration of cholesterol exposure or severity of vascular injury may also have differing effects on sensitivity to agonists.

While acute cholesterol elevation sensitizes vessels to norepinephrine, this may wane as atherosclerosis and sensitization to serotonin develops. In support of this, Henry and Yokoyama and Yokoyama et al have demonstrated that ergonovine-induced constriction in normal rabbit aorta is antagonized by \(\alpha\)-adrenoceptor blockade, while the enhanced constriction of atherosclerotic aorta to ergonovine is antagonized by serotonin blockade with cyproheptadine. These results suggest that atherosclerotic blood vessels are supersensitive to ergonovine and that this may occur via a shift from adrenergic control to serotonergic control. These results may also help explain the efficacy of ergonovine in provoking coronary vasospasm.

An ideal animal model for the study of vasospasm remains to be developed. However, recent studies in intact animals have concentrated on the combination of balloon-catheter denudation of coronary arteries and high cholesterol feeding. This regimen used in miniature swine produces atheromatous lesions in the coronary artery similar to that seen in humans and also produces angiographically documented coronary spasm in response to large doses of histamine. That study, in contrast to studies in humans, failed to demonstrate spasm in response to ergonovine. A similar study reported enhanced constriction of canine coronary arteries in vivo to ergonovine following balloon injury and elevated dietary cholesterol. Following sacrifice, the isolated vessels from this study were supersensitive to ergonovine and serotonin, but not phenylephrine, supporting the involvement of serotonergic mechanisms. Thus, the majority of studies in experimental animals have suggested that atherosclerosis contributes to vascular hyperactivity via the enhancement of serotonergic mechanisms. Yet the inability to demonstrate spasm similar to the human condition indicates that other factors are involved.

Future Directions and Conclusions

The research work to date in this field has emphasized basic mechanisms of the control of coronary artery vasomotion, with the hope of extrapolation of this knowledge to the understanding of pathological states in patients with a variety of coronary artery disorders. Unfortunately, the research in patients and experimental animals has not convincingly shown that the experimental preparations are entirely relevant to that observed in the clinical setting. Accordingly, a reliable and relevant model for the study of human coronary artery vasospasm would be extremely useful but is not currently available.

The bulk of experimental work to date on control of large coronary artery has been limited to the administration of exogenous agents and assessment of their effects on vascular control. However, there are several important areas that have only superficially been explored. The recent work by Barger et al suggests that vasospasm may be associated with an enhanced vascularization of the smooth muscle surrounding an atherosclerotic plaque, and that intramural as well as intraluminal events may be responsible for vasospasm. Furthermore, most previous work has been conducted using pharmacologic stimuli. It will also be important to study mechanisms by which autonomic neural mechanism control large coronary caliber, especially with respect to autonomic interactions with the endothelium and atherosclerotic vessels. Finally, in addition to examining stimuli that are responsible for changes in vascular reactivity, it will be important to determine potential alterations in the transduction mechanisms by which vascular smooth muscle responds to these stimuli. One example is the extensive work attempting to isolate and characterize the nature and structure of EDRF. Questions also exist regarding changes in the molecular biology of contractile proteins, ion channels, membrane receptors, and alterations in membrane fluidity.

It is now clear from both in vitro studies and in vivo preparations that large coronary arteries are not simply passive conductive vessels responding solely to changes in arterial pressure, but also undergo active vasodilation and vasoconstriction. The large coronary arteries respond to a variety of autonomic and pharmacologic stimuli. It is most important to keep in mind that in the intact animal any direct effect of a vasodilator or vasoconstrictor is modified not only by pre-existing autonomic tone, but also by the vasodilating properties of the endothelium and changes in coronary blood flow. It is this important point that helps explain much of the controversy that has arisen over control of large arteries. Since the endothelium is easily disrupted, manipulation of large coronary arteries for isolated vessel studies or acute implantation of transducers to assess vasoactivity in vivo can affect endothelial integrity and distort the responses to a variety of pharmacologic interventions. The future research regarding control of large coronary arteries should concentrate not only on basic mechanisms, but also on the manner in which these mechanisms interact in normal and diseased vessels, since large coronary vasoactivity is affected significantly by pathologic factors, e.g., damaged endothelium, elevated cholesterol, atherosclerosis, and platelet function.

Acknowledgements

The authors would like to thank Professor Dr. Eberhard Bassenge and Dr. Thomas Hintze for their careful review of the manuscript.

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Key Words • large coronary arteries • coronary artery vasospasm • vasodilation
Regulation of large coronary arteries.
M A Young and S F Vatner

Circ Res. 1986;59:579-596
doi: 10.1161/01.RES.59.6.579

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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