Adrenergic Responses of the Coronary Vessels

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THE EFFECTS of stimulation of the cardiac sympathetic nerves and of circulating catecholamines on the heart and coronary circulation have been studied extensively for more than 80 years. The biochemical, electrophysiological, and mechanical responses of the myocardium have been described in considerable detail but surprisingly little is known about the adrenergic responses of the coronary vessels. This is because of the difficulty in separating the direct actions of adrenergic agents on coronary smooth muscle in the intact animal from the secondary effects induced by the almost simultaneous changes in transmural pressure and myocardial metabolism. A common approach to the problem of separating these effects has been to use adrenergic agents which selectively stimulate or block specific myocardial or coronary adrenotropic receptors. It therefore is appropriate to begin with a brief outline of the classification of these receptors.

Adrenergic Receptors

Adrenergic motor responses fall into two groups according to the relative ability of various agonists to induce them. In one group the relative potencies of epinephrine (E), norepinephrine (NE), and the synthetic agent isoproterenol (ISO) are E > NE > ISO. Responses of this type were postulated by Ahlquist to result from stimulation of receptors which he arbitrarily designated alpha. The order of agonist potency for the second group of responses was ISO > E > NE and the receptors involved were designated beta. This dual receptor hypothesis gained much support from the discovery of relatively specific blocking agents for each of the receptor types. Thus phenoxybenzamine blocks alpha-receptors but has little effect on beta-receptors. On the other hand propranolol blocks beta-receptors with little effect on alpha-receptors. In the cardiovascular system, vasoconstriction is mediated by alpha-receptors, since the vasoconstrictor potency of NE and E is much greater than that of ISO, and the response is blocked by phenoxybenzamine. Vasodilation and myocardial inotropic and chronotropic responses are mediated by beta-receptors, since ISO is the most potent agonist and the responses are blocked by propranolol. However, the myocardial beta-receptors are somewhat unusual in that E and NE are approximately equipotent whereas E is very much more potent than NE in stimulating other beta-receptors such as those in the bronchi and skeletal muscle arterioles. Recently myocardial and other beta-receptors have been further differentiated by their responses to certain new adrenergic agonists and antagonists. For example, the drug salbutamol is only 2-15 times less potent than ISO as a peripheral vasodilator but is 100-600 times less potent than ISO as an inotropic agent. Propranolol does not differentiate the myocardial from smooth muscle beta-receptors, since it is equally effective in blocking myocardial stimulation, bronchodilation, and vasodilation. On the other hand, low concentrations of another beta-adrenergic blocking agent, practolol, block the myocardial responses to ISO but considerably higher concentrations are required to block ISO-induced bronchodilation and vasodilation. These and other differences have led to the subdivision of the beta-receptors into beta-1 (myocardial) and beta-2 (other) types. Some of the major differences between the beta-1 and beta-2 receptors are shown in Table 1. Although this oversimplifies a subject of considerable pharmacological complexity, it should assist the reader to follow the various in vitro and in vivo studies which have attempted to characterize the coronary vascular adrenotropic receptors.

Effects of Adrenergic Amines in Vitro

These studies usually have involved the measurement of the force developed after the addition of adrenergic agents by isolated coronary arterial strips or rings bathed in physiologic salt solutions. An alternative method has been to measure the changes in resistance of isolated perfused coronary arterial segments when adrenergic amines are injected. The presence of alpha-adrenotropic receptors in the larger coronary arteries of several species, including man, has been unequivocally demonstrated, since NE and the relatively pure alpha-adrenergic agonist phenylephrine produce constriction which is blocked or reversed by alpha-adrenergic blocking agents. In contrast, smaller arteries (100-500 μm) have extremely weak alpha-receptor activity, since they are not appreciably constricted by NE or phenylephrine. A weak constrictor response may, however, be unmasked by beta-adrenergic blockade. The existence of coronary arterial beta-adrenotropic receptors has also been convincingly shown, since ISO, NE, and E relax both large and small coronary arteries in which vasoconstrictor tone has been induced by high potassium solutions or by acetylcholine. This relaxa-
Coronary vasodilation occurred in association with the developing myocardial stimulation. There has been one study of intracoronary NE in anesthetized man. This showed that the injection of NE into vein grafts after bypass surgery produced a marked but transient reduction in coronary flow. The magnitude of the response suggested that coronary arteriolar constriction had occurred but the possibility that the effect was due to constriction of the vein graft was not excluded. Several investigators have studied the effects of intracoronary NE in dogs pretreated with agents which block both β-1 and β-2 receptors. Constrictor responses to NE were enhanced and dilator responses were reversed. Taken together, these experiments indicate that NE simultaneously activates both α- and β-receptors in the coronary vasculature. Intracoronary E resembles NE but more consistently produces initial dilation, suggesting a greater ability to activate coronary β-receptors. Intracoronary ISO dilates the coronary resistance vessels in arrested perfused hearts, in beating hearts in anesthetized dogs, and in conscious dogs, and in anesthetized man after coronary bypass surgery. When the heart is beating, coronary flow begins to increase before any effects on the myocardium or arterial pressure become manifest. Very low doses produce coronary vasodilation in the complete absence of inotropic or chronotropic effects. These responses clearly indicate the presence of β-adrenergic receptors in coronary arteriolar smooth muscle. Many studies indicate that they are of the β-2 type since low doses of practolol block the inotropic action of ISO more readily than the coronary vasodilator response.

### Effects of Adrenergic Amines in Vivo

These studies have usually inferred the effects of adrenergic stimulation on coronary smooth muscle from the changes in coronary vascular resistance in hearts perfused at constant pressure or flow. A variety of β-adrenergic blocking drugs has been used to reduce or eliminate the adrenergic responses of the myocardium. Coronary vascular responses have also been studied in perfused arrested or fibrillating hearts.

The effects of intracoronary NE vary according to the experimental preparation. An initial constriction followed by dilation is produced in arrested or fibrillating hearts. A similar response occurs in anesthetized dogs with beating hearts, although in some studies an initial constriction was not observed. Only one investigation of the effects of intracoronary NE in conscious dogs has been reported. Three dogs were used. The initial response was constriction in one dog, dilation in another, and no change in a third. Subsequently coronary vasodilation occurred in association with the developing myocardial stimulation. There has been one study of intracoronary NE in anesthetized man. This showed that the injection of NE into vein grafts after bypass surgery produced a marked but transient reduction in coronary flow. The magnitude of the response suggested that coronary arteriolar constriction had occurred but the possibility that the effect was due to constriction of the vein graft was not excluded. Several investigators have studied the effects of intracoronary NE in dogs pretreated with agents which block both β-1 and β-2 receptors. Constrictor responses to NE were enhanced and dilator responses were reversed. Taken together, these experiments indicate that NE simultaneously activates both α- and β-receptors in the coronary vasculature. Intracoronary E resembles NE but more consistently produces initial dilation, suggesting a greater ability to activate coronary β-receptors. Intracoronary ISO dilates the coronary resistance vessels in arrested perfused hearts, in beating hearts in anesthetized dogs, and in conscious dogs, and in anesthetized man after coronary bypass surgery. When the heart is beating, coronary flow begins to increase before any effects on the myocardium or arterial pressure become manifest. Very low doses produce coronary vasodilation in the complete absence of inotropic or chronotropic effects. These responses clearly indicate the presence of β-adrenergic receptors in coronary arteriolar smooth muscle. Many studies indicate that they are of the β-2 type since low doses of practolol block the inotropic action of ISO more readily than the coronary vasodilator response.

### Comparison of Results of in Vivo and in Vitro Studies

The majority of in vitro studies seem to indicate that the coronary vascular receptors are β-1, whereas the majority of in vivo investigations indicate that they are β-2. However, the in vivo studies mainly reflect the responses of "resistance" vessels, i.e., those less than 100 μm in diameter.
whereas the in vitro studies have been made on much larger vessels. Until methods have been developed to determine the reactivity of the large coronary arteries in vivo, the significance of the in vitro results must remain speculative. Incubation of vessels in physiologic salt solutions may alter the reactivity of the receptor sites, the relative efficiency of the uptake, and biotransformation of the various agonists and antagonists, and may also influence the processes which couple receptor occupation to muscle relaxation.

Adrenergic Neural Responses

The heart and coronary circulation receive a plentiful sympathetic nerve supply. When these nerves are stimulated coronary blood flow invariably increases, although this increase is often preceded by a very brief initial reduction in coronary flow in conscious and anesthetized dogs. The initial transient vasoconstriction is enhanced by β-adrenergic blockade with propranolol or propranolol and is abolished by phenoxybenzamine.

The effects of reflex sympathetic stimulation on the coronary circulation have received only slight attention. Reduction of carotid pressure in anesthetized dogs increased heart rate, systemic arterial pressure, and coronary blood flow. Coronary vascular resistance was unchanged or decreased. When the chronotropic and inotropic effects were prevented by pretreatment with propranolol, carotid occlusion caused arterial pressure to rise to a greater extent than coronary flow, indicating that coronary vascular resistance had increased. These results suggest that baroreflex activation of the coronary sympathetic nerves tends to constrict the coronary resistance vessels and that this tendency is normally balanced or overcome by the metabolic dilation secondary to myocardial stimulation. Carotid sinus nerve stimulation in conscious dogs with paced hearts caused weak coronary vasodilation which was blocked by guanethidine and phenoxybenzamine but not by propranolol or atropine. This suggests the existence of weak sympathetic coronary vasoconstrictor tone.

Adrenergic Agents and the Distribution of Coronary Flow

The distribution of coronary flow within the left ventricular wall is uniform in anesthetized dogs, and the ratio of flows to the inner (subendocardial) and outer (subepicardial) regions is approximately unity. Systolic flow in the left ventricular subendocardium is probably negligible because of extravascular compression, whereas appreciable systolic flow occurs in the subepicardium. Since average flow is at least as high in the subendocardium as in the subepicardium, the resistance of the subendocardial vessels must be lower, probably because the arterioles are more dilated. This is of great significance in understanding the effects which adrenergic stimuli produce on coronary flow distribution.

Intravenous infusions of ISO in doses which do not cause marked hypotension or tachycardia do not alter the inner/outer flow ratio. The increased myocardial oxygen demands are met by uniform arteriolar dilation which causes inner and outer flows to increase equally. Doses of ISO which produce substantial hypotension or tachycardia cause the inner/outer flow ratio to fall because subendocardial flow does not increase to the same degree as subepicardial flow. This presumably occurs because the subendocardial vessels reach maximal dilation earlier and subendocardial flow then declines as aortic diastolic pressure falls and diastole shortens. The relative underperfusion of the subendocardium is associated with impaired myocardial performance, lactate production, and abnormal electrocardiographic (ECG) changes. Stellate ganglion stimulation also reduces the inner/outer flow ratio but, because aortic diastolic pressure is maintained or increased, the relative underperfusion of the inner layer appears to be less than that produced by ISO. Propranolol reduces mean coronary flow in anesthetized dogs but the slower heart rate, reduced contractile force, and longer diastole favor inner layer perfusion which falls to a lesser extent than outer layer flow, and so the inner/outer flow ratio increases.

The changes in intramural coronary flow distribution produced by adrenergic stimulation are largely explicable on
the basis of hemodynamic changes and the associated alterations in regional myocardial oxygen requirements. It would be of considerable interest to know whether intracoronary adrenergic agents or cardiac sympathetic nerve stimulation would produce changes in coronary blood flow distribution in the presence of a selective $\beta$-1 blocking agent. This would eliminate myocardial responses and provide evidence bearing on the distribution of coronary vascular adrenotropic receptors through the ventricular wall.

Unfortunately, none of the experiments on the effects of adrenergic agents on coronary flow distribution has been performed on conscious animals. It has recently been shown that the inner/outer flow ratio is 1.4–1.6 in awake dogs, much higher than in anesthetized dogs. This presumably will significantly affect the degree of systemic hemodynamic disturbance required to produce impaired subendocardial perfusion.

**Physiological Significance of Coronary Adrenergic Responses**

The range of sympathetic neural control of the coronary vasculature appears to be small. There is evidence that sympathetic activity produces tonic coronary vasoconstriction in conscious dogs but inhibition of this tone by baroreceptor nerve stimulation or by lung inflation reduces coronary vascular resistance only 20–50%. Insufficient evidence exists to assess the direct effect of sympathetic nerve stimulation on coronary smooth muscle in conscious dogs because the only reported study was not designed to separate the direct and indirect effects. However, intravenous NE infusions at rates within the physiological range increase coronary vascular resistance by 13–14%. The significance of the vasoconstrictor tone and the adrenergic constriction which develops during NE administration is obscure. Both would oppose the metabolic dilator influences on the coronary arteries and cause lower flow and a decreased myocardial $P_{O_2}$. It is difficult to imagine any beneficial consequences of these effects.

The physiological role of the coronary $\beta$-adrenotropic receptors is even less clear. It never has been unequivocally shown that sympathetic nerve stimulation can produce direct relaxation of coronary smooth muscle. When procyclin is administered to anesthetized dogs in doses which block myocardial $\beta$-1 responses, sympathetic nerve stimulation produces coronary constriction despite the fact that the $\beta$-2 receptors remain unblocked, as shown by their ability to mediate substantial coronary vasodilatation in response to ISO. The sympathetically induced constriction is not enhanced by subsequently blocking the $\beta$-2 receptors with propanolol. These observations strongly suggest that neurally released NE does not activate coronary vascular $\beta$-2 receptors in the anesthetized dog. The situation in conscious animals has not yet been tested. There is also a lack of convincing evidence that the coronary $\beta$-receptor response to circulating catecholamines has any physiological importance. The coronary circulatory effects of physiological infusion rates of E and NE in the presence of selective $\beta$-1 receptor blocking agents have not yet been determined in conscious animals. Bolus intracoronary injections of NE after low doses of propranolol always produce coronary vasoconstriction in anesthetized dogs. Under similar conditions the coronary dilator action of E is greatly reduced or abolished, suggesting that E activates coronary vascular $\alpha$- and $\beta$-2 receptors almost equally so that there is little resultant change in arteriolar diameter.

**Concluding Remarks**

It is clear that more work needs to be done to establish the role of the adrenergic responses of coronary smooth muscle, particularly in conscious animals. No doubt improved methods of determining total and regional blood flow and myocardial oxygen consumption, together with use of more selective adrenergic blocking agents, will resolve some of the questions. Hopefully, the development of noninvasive methods may eventually enable the adrenergic response of the human coronary circulation to be assessed. These studies will have more than theoretical interest, since adrenergic activity has important implications in many facets of coronary disease, including coronary arterial spasms, collateral blood flow, infarct size, and cardiogenic shock.

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