PHARMACOLOGY OF THE CORONARY CIRCULATION

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The literature in the past year or two has given ample evidence that the investigation of the coronary vasculature is progressing rapidly from a very rudimentary level to a much more sophisticated one both in theory and applied methods. It is also evident, however, that the goal of understanding the molecular events comprising the nutritional circulation of the myocardium remains elusive.

As opposed to the mid 1960s, one is no longer concerned with coronary flow per se, but rather with endocardial vs epicardial flow; with arteriolar vs arterial flow; and with total vs (capillary) "nutritional" flow. One is no longer concerned simply with the level of adrenergic activity in "the heart," but rather with myocardial vs coronary adrenergic activity. There is even a suggestion that the alpha and beta receptor classification may warrant a major conceptual revision.

Methods of investigation have become more sophisticated. The perfection of techniques such as the Rb^{84} clearance developed by Renkin (1, 2) have allowed separate assessment of the nutritional (capillary) coronary blood flow. Ability to observe the microcirculation "in situ" and to quantify metabolic changes therein accurately by the stable oxygen electrodes originally developed by Clark (3–5) has permitted an appreciation of how changing tissue oxygen requirements can modify flow in a regional manner. The advent of reliable, miniaturized telemetry systems has led to a greater number of experimental studies carried out in unanesthetized, unrestrained animals (6, 7). Other techniques using variations of cardiopulmonary bypass have allowed assessment of the effects of flow independent of pressure and vice versa (8).

From a practical, clinical standpoint there are a limited number of categories of pharmacological agents of interest to the physician, namely vasodilators, the adrenergic blockers, the cholesterol lowering compounds, and anticoagulants. From the investigative viewpoint, however, there may be agents that at present do not have clinical applicability, but that aid in delineating the metabolic nature and normal responsiveness of the coronary vasculature.

Since the recent major contributions seem to have been in the areas of the nature of the adrenergic activity of coronary arteries, and of the mech-

anisms of action of vasodilators and adrenergic blocking agents, most of the following discussion will be concerned with these subjects.

General

One of the ways in which the coronary vasculature differs from that in the periphery is in the degree of oxygen extraction. There is approximately a 75% extraction resulting in a normal A-V O_2 difference of about 11.4 vol.%. More and more data accumulate reinforcing the concept that in the myocardium, the primary determinant of coronary blood flow is the tissue oxygen requirement (9–11). Coronary flow can, in turn, be a major determinant of myocardial contractile force (12).

Ischemia, completely independent of intact neural pathways, produces coronary vasodilatation, which has been demonstrated to take place in the arterioles. It has also been shown that this ischemia-induced dilatation can achieve maximal proportions in only ten seconds after complete circulatory arrest (13). Berne and his associates advocate that this ischemic response is mediated via adenosine, which is released from the myocardial cells (14–16). Other investigators have concurred in the opinion that a blood-borne factor is operative in this situation (10). Excellent studies by Duling & Berne (17) using micro-circulatory techniques have made it clear how very small changes in pressure-flow relationships by means of variation in local arteriolar resistance can result in large alterations in oxygen extraction. This variation in local arteriolar resistance can be brought about by the direct effect of oxygen on vascular smooth muscle. Ischemia (hypoxia) also seems to be a major requirement for stimulation of the development of collateral circulation (18). The concept that coronary vasodilatation occurs in response to local ischemia (from any cause) and is independent of neural control, is essential to an understanding of the coronary circulation.

Vasodilators

Given, therefore, the premise that flow in the coronary circulation may be governed by either local or central influences which in turn may be neural, mechanical, or

sodilators must be raised. First, if angina pectoris really represents local (or generalized) myocardial ischemia, and if there is normally a maximal autoregulatory vasodilatation in response to such a stimulus, why are nitrates effective in angina? Second, why are certain compounds such as dipyridamole and its derivatives, which are far more potent vasodilators than the nitrates, not effective in angina patients? Third, are diseased coronary arteries in man responsive to vasodilators in the same way as essentially normal coronary arteries in laboratory animals used in investigation?

A key concept in understanding this problem is that not all vasodilators act in the same area (19). Fam & McGregor (20) demonstrated that the coronary arterial supply could be functionally divided into the larger con-

ductive vessels and the smaller precapillary resistance arterioles, the site of the autoregulatory phenomenon. Angina is presumably caused anatomically by relative occlusion of the larger vessels, and these segments are the ones specifically dilated by the nitrates. Dipyridamole, on the other hand, acts on the arteriolar level rather than on the conductive vessels. It was shown that when arterioles dilate maximally secondary to ischemia, the nitrates cause further dilatation at the level of the larger conductive arterial segments (21). Winbury and his associates have also demonstrated that there is a gradient in myocardial oxygen tension which exists from the subepicardium (26mm Hg) to the subendocardium (17mm Hg), and that redistribution of flow to these regions may occur in response to various agents. The appreciation of differential oxygen availability is essential in understanding the mechanism of action of the anti-anginal group of drugs (19, 22, 23). Specifically, in experiments with dogs, nitroglycerin produced a selective increase in subendocardial oxygen tension in the absence of a change in total coronary flow, whereas dipyridamole, although increasing total coronary flow, did not significantly change the oxygen tension in either subendocardium or subepicardium.

This group has also shown that in dogs having an area of ischemic myocardium secondary to gradual constriction of the left anterior descending coronary artery, nitroglycerin increased myocardial oxygen tension in the ischemic area without changing oxygen tension in adjacent, normal myocardium. Dipyridamole, however, actually decreased oxygen tension in the ischemic area, but usually increased it in the normal area. Thus nitroglycerin can cause a favorable redistribution of myocardial blood flow without changing total coronary blood flow. This point is vital in understanding how nitroglycerin might benefit a patient with angina and atheromatous, nonreactive coronary arteries.

The studies of Mason et al (24), based on the earlier work of Williams et al (25), are concerned with the peripheral vascular effects of the nitrites and are important in explaining their clinical benefit in patients with angina pectoris. It is pointed out that in angina, which is secondary to ischemic myocardium, the coronary vasculature may be maximally dilated on the basis of the intrinsic vascular response to hypoxia. The relief of pain with sublingual nitroglycerin is secondary to a reduced myocardial oxygen requirement. The nitrates accomplish this on a peripheral vascular basis in two ways. By decreasing arterial blood pressure the cardiac afterload is decreased. In addition, ventricular filling (preload) is reduced by a peripheral venodilatation that decreases venous return. The heart size is thus reduced.

The fact, therefore, that nitrites relieve the pain of angina pectoris in patients most likely having nonreactive, atheromatous segments of their coronary arteries can be explained on two bases: a redistribution of flow within the heart itself, which does not require an increase in total flow, and a peripheral vascular effect that reduces the myocardial oxygen requirement by decreasing heart size and arterial blood pressure.

Autonomic Activity

The complete understanding of the innervation of the myocardium and coronary vessels has continued to pose problems in theory as well as in actual investigative protocols. One need only observe how well animals with autotransplanted hearts, or (not withstanding the rejection problem) human beings with cardiac homotransplants function, and the question arises: What *is* the function of the autonomic innervation of the myocardium and coronary vasculature? An obvious answer may be that the changes following cardiac denervation vs those following skeletal muscle denervation are so subtle that we have been able to detect only a few thus far (26). There is evidence that the changes following extrinsic cardiac denervation may be thought of in terms of "efficiency" rather than in terms of all-or-none work output (9, 27). Another possibility is that in view of the "intrinsic innervation" that remains (28), there may not be sufficient alteration of the presynaptic apparatus to effect a detectable post-synaptic or effector cell change. It will become apparent that the autonomic innervation of the coronary vasculature is quite different in many ways from its peripheral counterpart.

Krokhina (29) has provided evidence on an anatomical basis that the adrenergic component of the myocardial and coronary vasculature innervation matures earlier than does the cholinergic. Unlike the cholinergic, the adrenergic fibers going to form the effector plexus of the contractile element course along the coronary vessels with the neural elements supplying the vasculature. The vascular plexus and the pre-terminal adrenergic plexus of the myocardium form a unique interacting innervation structure. The role of vascular innervation, cholinergic and adrenergic, on basic reactivity of the coronary blood vessels needs further clarification.

Traditionally, when one thought of or investigated the autonomic system there was a separation of the adrenergic and cholinergic components, but perhaps this is no longer justified. The controversy surrounding the Burn-Rand cholinergic link theory (30) continues. This theory proposes that the action potential in a post-ganglionic sympathetic axon triggers the release of acetylcholine, which then releases norepinephrine from the nerve terminals. New anatomical evidence from Jacobowitz (31), however, would suggest that there are adrenergic elements present in cholinergic ganglia. The exact nature of their function remains conjectural, but the investigator believes that they represent a modifier principle in ganglionic transmission. That is, the adrenergic system may be able to influence, by these elements, the number or direction, or both, of synaptic transmissions through the ganglia.

Concerning cholinergic influences, Blesa & Ross (32) demonstrated that intracoronary acetylcholine in open-chest dog preparations results in a coronary vasodilator response mediated through muscarinic type receptors. Feigl (33), again in an open-chest dog preparation, demonstrated direct

parasympathetic coronary vasodilatation that resulted from vagal stimulation that was apparently independent of vagal inotropic and chronotropic myocardial effects. Ross & Blesa (34) have demonstrated that small intracoronary doses of nicotine (not enough to produce measurable systemic effects) produce a simultaneous increase in coronary flow and positive myocardial inotropic effect. The increase in coronary flow was secondary to a decreased coronary vascular resistance (vasodilatation) as well as to a lengthening of the diastolic period. The flow changes, which were identical to those produced by norepinephrine, could be blocked by propranolol, which suggested that the nicotine effect was mediated by catecholamines. The nicotine responses were also blocked by intravenous pentolinium, a ganglionic blocker. The inhibition of nicotine in these experiments by a beta adrenergic blocker was interpreted by the authors as evidence for the "cholinergic link" theory. According to this theory nicotine would have entered the post ganglionic fibers and indirectly (via acetylcholine) caused the release of catecholamines.

Concerning adrenergic influences, the question continues to be posed: Are there both alpha and beta receptors in the coronary arteries? Recent work would seem to answer "yes" (35–38), but the difficulty in demonstrating alpha receptors in coronary arteries points up another difference between the coronary and systemic vasculature.

Ross & Jorgensen (39) as well as McRaven et al (40) have recently demonstrated the myocardial adrenergic receptors may be experimentally separated from those of the coronary vasculature. In addition, McRaven et al contributed to the understanding of direct vs indirect effects of the catecholamines on the coronary vasculature. In this particular discussion "indirect" refers to coronary vasodilatation produced by the increased local myocardial oxygen requirement resulting from the direct positive inotropic and chronotropic effect of the catecholamines on the myocardium. It does not pertain in the usual pharmacological sense of a catecholamine-releasing property. Their experiments were based on the use of practolol, 4-(2-hydroxy-3-isopropylaminopropoxy) acetanilide, which in the doses used, is said to block myocardial but not vascular beta receptors.

As has been well-established in previous work, infusions of isoproterenol, norepinephrine, epinephrine, or sympathetic nerve stimulation will cause coronary vasodilatation associated with increases in left ventricular dp/dt, heart rate, and systolic pressure (23, 39, 40–42). In these experiments, following practolol, the coronary vasodilation following isoproterenol was reduced by about 30%, but occurred without changes in left ventricular dp/dt, systemic pressure, or heart rate. Furthermore, the remaining 70% of the coronary vasodilator activity could be eliminated by propranolol. After practolol, infusion of norepinephrine or sympathetic nerve stimulation resulted in coronary constriction and no change in dp/dt, heart rate, or systemic pressure. This constriction could be blocked by the alpha blocker phentolamine.

The authors interpret their results to mean that the coronary vasodilatation produced by norepinephrine and sympathetic nerve stimulation is primarily indirect and secondary to stimulation of the myocardial beta receptors. These two stimuli do possess some direct coronary vascular effect that is alpha in nature (vasoconstriction), but minimal in degree. They support, therefore, the concept of alpha receptor activity in the coronary arteries, but which is of much less degree than in the peripheral vasculature.

In regard to isoproterenol, the coronary vasodilator response appears to be both direct and indirect. In their preparation, which used anethetized dogs, the direct effect on the coronary vasculature predominated, rather than the indirect effect on the myocardial receptors.

Clinical experience over the past five years would seem to indicate that the beta adrenergic blocker, propranolol, is effective in the treatment of patients with angina pectoris (43, 44). Having discussed the effect of adrenergic stimulation on the coronary vasculature and its concommitant effect on the myocardial oxygen requirement, we can now consider the mechanisms underlying the clinical effectiveness of beta blockade.

In the excellent review by Epstein & Braunwald (45) the work of Nayler et al (46) and others was examined and it was noted that the decreased coronary blood flow following propranolol was secondary to a decreased myocardial oxygen requirement. This was the result of the decreased arterial blood pressure, heart rate, and velocity of contraction produced by the beta adrenergic blocking agents. This, in turn, produced an increased coronary vascular resistance and decreased coronary blood flow. Angina is presumably precipitated by increased myocardial sympathetic activity and oxygen needs that cannot be met because of an impaired circulation. Thus propranolol could be effective solely on a beta blocking basis. The experiments by Somani et al (23) have shown, however, that catecholamines cause a redistribution of coronary blood flow in such a manner that regional flow to the endocardium is selectively decreased. This occurs at a time when total coronary flow remains unchanged. This also provides an explanation for the localization of necrosis following catecholamine infusions to the region of the endocardium. The beta blocking drugs, therefore, in addition to their other effects, may aid by preventing this deleterious redistribution of blood flow that causes a relative ischemia in the endocardium (47).

It has been recognized by clinicians that the nitrates and beta adrenergic blockers are synergistic in their relief of anginal pain (44). As pointed out by Mason et al (24) and others (43), the essential element in this pain relief is the reduction of the myocardial oxygen requirement. The nitrites and propranolol reduce this requirement by entirely different mechanisms and thus would be synergistic. The nitrites, in addition to a local redistribution of myocardial flow, and decrease in arterial blood pressure (afterload), cause a reduction in ventricular size secondary to a decreased venous return (preload). Propranolol, on the other hand, inhibits sympathetic stimulation

caused by exercise as well as the reflex increase in sympathetic activity that results from the hypotensive action of the nitrites.

Synthesis of new beta blocking drugs continues. The goal in mind is always the same, that being more beta-blocking activity with less direct myocardial depressant activity. Among them, sotalol (MG-1999), Ciba, 30,089-Ba, ICI 50, 172, and practolol (mentioned above) have all been tried experimentally, but propranolol continues to be the compound used clinically.

An original and fascinating theory has been proposed by Kunos & Szentivanyi (48) which would alter the basic conception of the Ahlquist classification (49). This "modulation theory" suggests that instead of separate alpha and beta receptors, there is a single receptor present, the characteristics of which may be modified (or modulated) by changing metabolic conditions. In their original study in isolated hearts they demonstrated a marked change in the alpha and beta receptor blocking capabilities of phentolamine and propranolol respectively by changing the temperature of the preparation. Another paper describing experiments in the innervated dog hind limb preparation offers additional data to support this theory (50). Under control conditions, norepinephrine elicited a marked vasoconstriction, as expected, which could be blocked by alpha adrenergic blockers. When striated muscles were active, however, the constriction effect disappeared, but could be restored with beta adrenergic blockers. After the administration of an alpha blocking agent, the beta blocking agent was no longer able to restore the resting alpha state. The authors propose that a transformation of receptor activity occurs by means of a substance produced by the muscle activity. Coronary sinus blood of donor dogs being sympathetically stimulated produced the same effect in recipient dogs as muscular activity. It is proposed that an organ such as the heart would have its receptor activity modulated by the high level of metabolic activity. This would offer an explanation for the difficulty in demonstrating alpha activity in the intact heart and coronary vasculature. Also, in the diseased state in man an alteration in the metabolic conditions local to the vasculature and receptors could provide a reason for changes in myocardial and vascular reactivity.

Broadley recently analyzed the coronary response to catecholamines in a modified Langendorff preparation (51). In his experiments he pays particular attention to the time course of events following intracoronary infusion of catecholamines. Although he saw the "traditional" vasodilatation seen by others (and blocked by propranolol), he noted an initial constriction, blocked by phentolamine and evident along with threshold doses of epinephrine. This observation is cited as further evidence of the existence of alpha receptors in the coronary vasculature.

Other Vasoactive Substances

In the area of nonautonomic vasoactive substances, glucagon (52–54) and angiotensin (55, 56) have received considerable attention. Gluca-

gon appears to have all the effects of catecholamines with regard to the coronary vasculature (i.e. decreased vascular resistance and increased total coronary flow), but is not affected by adrenergic blockade in small to moderate doses. There has been one difference noted in the pattern of response in the coronary vasculature, however, and that is that the ratio of systolic to diastolic flow remains unchanged after glucagon (52).

It should be kept in mind, however, that Glick et al (57) have shown that glucagon has little direct effect upon the peripheral vasculature. Therefore, until its reaction upon the coronary vasculature can be studied in the nonworking heart, the possibility exists that the effects documented thus far may be secondary to an increased myocardial oxygen consumption.

The recent study by Drimal et al (56) demonstrates that angiotensin II has a direct effect on the coronary vascular smooth muscle in the anesthetized dog preparation which results in vasoconstriction and a decrease in myocardial contractility. He notes a second phase in which there is an increase in myocardial contractility. He attributes the positive inotropic response of the second phase to released catecholamines. More recent evidence (55) would seem to indicate that angiotensin, in addition to its well-documented indirect effects, elicits a direct myocardial positive inotropic effect that is independent of endogenous catecholamines.

Although the existence of the prostaglandins has been known for over thirty years (58), thorough investigation of their cardiovascular effects has only been undertaken recently. Although it was known that certain groups of prostaglandins produced an increased coronary blood flow (59), limitation of techniques left it uncertain as to whether this was a direct or indirect effect. Higgins et al (60), however, have used conscious, unanesthetized, telemetered dogs to demonstrate that prostaglandin A_1 resulted in up to a 74% increase in coronary blood flow and a 61% decrease in coronary vascular resistance. In paced, beta blocked preparations it still resulted in a 42% decrease in coronary vascular resistance (vasodilatation) indicating that to a major extent this response is a direct vascular effect and not due primarily to increased metabolic requirements of the myocardium.

Kadowitz et al. (61) have demonstrated that prostaglandin F_{2a}, a known vasoconstrictor, and angiotensin can greatly potentiate the response of the saphenous vein to sympathetic nerve stimulation by different mechanisms. The authors propose that these substances may act as modulators in adrenergic neurotransmission. This particular type of approach would seem to be a fruitful area to investigate in regard to the coronary vasculature.

The kinins are another group of vasoactive substances receiving attention currently (62). The most widely known of these polypeptides is bradykinin. Although the functional role of these substances, especially in regard to the coronary circulation, is not fully known, there are several studies demonstrating bradykinin to be a potent coronary vasodilator independent of any myocardial effect (63, 64). Like angiotensin, another polypep-

tide, bradykinin can release adrenal catecholamines (65). Perhaps future studies will place it in a category with adenosine nucleotides as a normal metabolic modulator of the coronary vasculature.

Serotonin (5-hydroxy tryptamine) has long been known as a vasoactive substance (66). The vascular receptors sensitive to it appear to be different in nature from the adrenergic receptors, and in addition, depending upon the species tested, the preparation used, and the particular vessel examined, serotonin may act either as a vasodilator or a vasoconstrictor. In regard to the coronary vasculature, however, vasodilator effects have been described in the cat, dog, and rabbit hearts, and vasoconstrictor effects in the rat and pig heart (67). It is also known to have a direct myocardial positive inotropic effect that is dependent upon catecholamine stores. More precise work needs to be done, therefore, to determine whether the effect on the coronary vasculature is direct or indirect.

Digitalis, a clinically important drug usually employed for its direct myocardial positive inotropic effect, has been shown by Vatner et al (68) to have coronary artery constriction properties of moderate magnitudes. Digitalis, like nitroglycerin, although used in an effective manner clinically for almost a century, has only recently begun to be understood in terms of molecular or cellular mechanisms. [This study by Vatner et al (as well as the one by Higgins et al, 60, on prostaglandin A_1) clearly points up the rather marked differences that can result in experiments on awake vs anesthetized animals.]

An excellent review by Somlyo & Somlyo (69) covers all the vasoactive substances in relation to vascular smooth muscle in great detail.

Cholesterol Lowering Agents

Since the advent of lipid typing and the further understanding of the role of blood lipid content in the pathogenesis of atheromatous disease, there has been much interest in substances that clinically lower serum cholesterol (70, 71). There are now thousands of patients with coronary artery disease taking these drugs, but a major question still unanswered is whether an elevated serum lipid level is the principal cause of atheromatous coronary artery disease. In patients who do seem to be improved clinically another question to be answered is whether there is a favorable direct vascular effect of these drugs. There is no information to date that indicates any vasodilating properties, but there is some suggestion that with certain of these drugs improved flow may result from alteration in clotting mechanisms (72, 73). If large numbers of patients will be on this type of metabolically active drug for long periods of time, the possible interaction of these substances with coronary vasodilators, inotropic agents, and anti-arrhythmic agents may need to be evaluated.

Abrams & Gaut recently reviewed the current status of these drugs (74). Two substances that block intestinal absorption of cholesterol are the

sitosterols, which compete with cholesterol for absorption and are nonatherogenic, and cholestyramine, an ion-exchange resin which binds bile acids and therefore increases the fecal excretion of bile (cholesterol).

Of the substances that can interrupt cholesterol biosynthesis, clofibrate (ethy-p-chlorophenoxyisobutyrate) (Atromid-S) is the most widely used. It apparently acts in the first phase of cholesterol synthesis and disrupts the cycle between acetate and mevalonate. SaH-2348 is chemically similar to clofibrate and is nine times more active, but the clinical safety remains to be established.

Ay-9944 inhibits the third stage of cholesterol synthesis, and specifically inhibits the conversion of 7-dehydrocholesterol to cholesterol. Again, the clinical safety of this substance remains to be established.

Thyroid hormones, dextrothyroxine in particular, are known to lower blood cholesterol, but increase the propensity for angina and myocardial irritability in patients with atheromatous coronary artery disease—the very people who would be using a hypocholesterolemic agent.

Lastly, nicotinic acid has long been known to be effective in lowering serum cholesterol, but numerous minor although annoying side effects usually preclude wide clinical acceptance. The exact mechanism by which nicotinic acid works is still unknown.

Anticoagulants

It was originally thought that administration of anticoagulants soon after clinical evidence of myocardial infarction would decrease areas of extension and improve blood flow in marginal areas. As the results of long-term, carefully controlled clinical studies are tabulated, however, it would seem that the initial enthusiasm for the use of anticoagulants in myocardial infarction or angina pectoris, or both, was to some extent unfounded (75) (76). Though there is clearly a place for heparin and the warfarin derivatives in certain clinical areas, such as postoperative prosthetic heart valve patients, a good deal of evidence indicates that there is very little clear benefit derived from their routine use following myocardial infarction, although some would disagree (77, 78).

Additional Observations

The status of the coronary venous circulation may exert significant influence on regional or total coronary perfusion (79). However, very little has been reported on the reactivity of coronary venous vasculature to pharmacological agents. That this area remains relatively unexplored probably reflects the difficulty inherent in isolation and study of this portion of the vascular bed.

Progress in the development of methods and drugs to improve coronary blood flow, and its regional distribution in diseased states will be facilitated by the development of better animal models of the diseased, obstructed coronary circulation with impaired myocardial and circulatory performance.

The treatment of cardiogenic shock by mechanical support systems is receiving considerable attention. Various forms of arterial counterpulsation studied in normal hearts and those with a major coronary artery ligated have been reported to increase coronary blood flow while "unloading" the heart. This technology will not replace the need for pharmacological agents, but would be useful for limited applications in extreme states—at which time drugs might well be used in conjunction with circulatory assistance pumps.

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