PHARMACOLOGY OF THE CORONARY CIRCULATION[1]

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During recent years, there have been several reviews of coronary circulation and myocardial metabolism (1–5). The first three of these did not touch heavily on the pharmacology of the coronary circulation, however; and the last referred only to observations concerning pharmacologic agents on the heart of man. It is hoped that the present review will supply references to more specific data for those who require it, but no attempt will be made to review all available material. The grouping of agents will be quite artificial in some circumstances, but in an area so widely investigated, some manner of grouping is required.

Coronary Vasodilators

When coronary blood flow is considered, the first subject that invariably arises is that of coronary vasodilators, especially nitroglycerin. Consequently, systemic and coronary hemodynamic effects of nitroglycerin have been extensively investigated in both animals and man (6–19). Systemically administered to dogs with imbedded coronary flow probes, this agent generally produces a mild transitory increase in coronary blood flow accompanied by coronary vasodilatation (11–13). This is followed quickly by a reduction in coronary flow to or even below the level which preceded nitroglycerin administration. Continuing dilatation of the larger coronary arteries is seen whether the coronary arteries are examined directly or by arteriography (6–8). There are conflicting reports of the coronary hemodynamic effects of this agent in man, even though the large coronary arteries are consistently dilated (7). Thus, coronary flow has been reported to be increased in normal man, either when measured by the nitrous oxide method (14) or by coincidence counting (16). However, in human subjects with coronary artery disease or increased left ventricular work, no such increase was observed (15, 20). This discrepancy is difficult to understand since dilatation of vessels occurs, whether they are atherosclerotic or normal (7). Therefore, there is little reason to expect the action to be different in these groups. Furthermore, by the method of radioactive xenon clearance (17), and by clearance of sodium 24 after localized intramyocardial injection (21), nitroglycerin did not change coronary flow unless the drug was injected directly into the coronary arteries

[1] The survey of literature pertaining to this review was concluded in June, 1967.

(22). Intra-arterial injection into the coronary circulation is such an artificial situation that its results cannot be seriously considered to be related to usual systemic administration. Obviously, any vasodilator injected exclusively into one vascular bed in a dose which does not affect other blood vessels will cause local vasodilatation and a local increase in blood flow. Such data are not apt to be helpful in understanding the effects of a vasodilator when given systemically, unless there is reasonable evidence that the time distribution of action is different in the two vascular beds and that such a time differential is potentially important in drug action. Since the coronary arteries are the first vessels in the arterial circuit to be perfused, because of their anatomical position, it is conceivable that they might react first if the rate of rise in blood concentration of a vasoactive substance were sharp enough. The transitory localized vasodilatation which would take place prior to general vasodilatation and decreased systemic arterial pressure could explain the transitory increase in coronary blood flow which occurs in most coronary flowmeter studies (11-13, 23). When all of the body vessels susceptible to the drug have been dilated, perhaps equally, and a new steady state at a lower arterial pressure is reached, increased coronary blood flow would no longer be expected, and, according to most data, does not occur. Hemodynamic studies have been done by the nitrous oxide method after systemic administration of trolnitrate (18), pentaerythritol tetranitrate (18), erythrol tetranitrate (24), and isosorbide dinitrate (25). No increase in coronary flow was observed. As a result of the failure of the nitrate compounds to increase coronary flow during the time when anginal pain is relieved by their administration (15, 17–19, 24, 25), there has been much speculation as to their mechanism of action in the relief of the pain of angina pectoris and several additional factors may be considered.

It is generally agreed that the cardiac size decreases subsequent to administration of nitroglycerin (26–28). The tension required in the heart wall to produce a given arterial pressure is related directly to the square of the radius of the cardiac chamber (29, 30); therefore, reduction in cardiac size is associated immediately with reduction in the pressure-time work of the myocardium. The myocardial oxygen consumption is generally related to the force of myocardial contraction and the length of time this force is exerted. Such a concept can be expressed by relating cardiac oxygen consumption to the product of systemic arterial systolic blood pressure and cardiac rate (31), or to the integrated intraventricular pressure-time area (32), or probably more precisely to some expression containing the integrated intraventricular pressure-time area, the intracavitary left ventricular diameter and surface area, the thickness of the myocardium, and the rate and distance of movement of the left ventricular wall. The problems in securing accurate measurements are great, especially in intact subjects; consequently, at present, although the concept is clear, it is chiefly of academic interest. Conceding, then, that all of the desirable data are not available, it would appear that nitroglycerin should affect most of these factors in a manner

which should reduce myocardial oxygen consumption, and tend to correct any discrepancy between nutrient supply and demand, as well as to insure adequate clearance of metabolic products.

Nitrates also decrease venous pressure (14, 15, 24, 25), pulmonary artery pressure (14, 15, 18, 24, 25, 33), systemic arterial pressure, and cardiac output (14, 15, 18, 24, 28). There is evidence that elevation in systemic arterial pressure usually precedes the onset of anginal pain (34), and that pain tends to occur when a particular systolic pressure-rate product is reached (35). Relief of pain tends to occur when the pressure-rate product falls to a level which existed prior to the onset of anginal symptoms. It is difficult to decide whether the important factor in reduced blood pressure, which relieves angina, is chiefly related to reduced cardiac work, or whether the "throttling effect" of the left ventricular systole on its own circulation is reduced. The problem is complicated by the fact that the circulation to the inner portion of the myocardium comes at least in part from vessels which perforate the myocardium from its external surface (36) and is compromised to some extent during systole. This is presumably established since coronary flow increases when myocardial perfusion pressure is maintained and the heart is arrested (37), and since left ventricular coronary flow decreases sharply during systole (3). Unfortunately, it is not easy to determine what force is exerted on either the perforating vessels or the intramyocardial capillaries. The myocardium is not a fluid which transmits pressure equally in all directions, but contains connective tissue and myofibrils as geometric structures of greater and lesser rigidity. The myofibrils may well exert force parallel to capillaries rather than perpendicular to them and thereby, produce little or no constriction. Indeed, recent studies of blood flow in skeletal muscle have shown that if the amount of muscle shortening is not excessive, causing kinking and obstruction of vessels, blood flow actually increases during sustained forceable contraction (38). Therefore, at least in skeletal muscle, "extravascular compression," as a factor in controlling flow, may have been seriously over-estimated (39). The constricting effect in the heart, then, might be chiefly due to more superficial fiber layers. Much of the compression might be supported by the muscle fibers in their contracted and firm state, and the actual compression applied to the capillaries nestling protected between these fibers might be considerably less than systolic intraventricular pressure. Measurements of phasic coronary flow have been made by devices which are applied to coronary arteries on the surface of the heart, and these measurements may relate chiefly to inflow into the major vessels, not to the microcirculation. Allowing for the small volume of the coronary arteries, however, it is difficult to believe that the 30 per cent of coronary flow which may occur in systole (3) does not perfuse at least some myocardial capillaries. Conceivably, a slight change in systolic pressure level, accompanied by altered cardiac size or pattern of muscle contraction, could affect the distribution of blood flow considerably.

Dilatation of the major coronary vessels occurs on administration of

nitroglycerin (6–8), sometimes to the point of opening out segments of the arteries so they can be demonstrated by coronary arteriography when they could not be seen prior to its administration. Collateral vessels are also seen to dilate subsequent to administration of nitroglycerin. Whether they then carry more oxygen to the heart distal to areas of obstruction is not established in man, but it seems probable. Although it has been reported that myocardial oxygen tension, as measured by a platinum electrode, rises and then falls subsequent to nitroglycerin administration (19), it has recently been reported that after the administration of nitroglycerin, there is a sustained rise in the pO_2 of cardiac muscle in the area distal to an obstructed coronary artery (40). A refinement in this report is the use of the oxygen electrode which may well explain the differences between this study (40), that of Smith (41), who demonstrated little evidence for increased oxygenation in similar experiments, and other experiments which revealed no increase in back-bleeding from transsected coronary arteries (42, 43).

Although the concept of benign and malignant coronary vasodilators (44) expresses a useful physiologic concept, it means very little insofar as clinical application of drugs is concerned (45). Benign vasodilators, which increase coronary blood flow and elevate coronary sinus oxygen content (hydralazine, dipyridamole), frequently do not relieve anginal pain, and occasionally hydralazine may precipitate angina. Possibly, this is because the real resistance to coronary flow is normally in the arterioles, as it is elsewhere in the body. If, in angina, the resistance which controls flow becomes displaced into the diseased major coronary arteries, it is conceivable that a vasodilator which affects these trunks might produce redistribution of pressure within the major vessels so that each section of the myocardium can again control its own flow through usual arteriolar mechanisms (40). Thus, it is postulated that another factor in relief of angina by nitroglycerin may be through better distribution of the perfusing pressure, not only through collateral vessels but also through the partially obstructed main trunks themselves. In addition since nitroglycerin also decreases cardiac output (14, 15, 28), there are many acceptable reasons why it may be effective in relieving anginal pain even if it does not increase total coronary blood flow.

There are several coronary vasodilators which fall into the category of benign vasodilators, i.e. those that increase coronary flow without increasing myocardial oxygen utilization and, therefore, produce an increase in coronary sinus oxygen tension (44). Into this group fall dipyridamole (46–49), lidoflazine (50, 51), isoptin (52), and hexadylamine (53). Dipyridamole inhibits adenosine deaminase (54). Thus, it may increase coronary blood flow by sparing adenosine, a known potent coronary vasodilator (55–57). It has long been postulated that adenosine, or a closely related vasoactive substance, may be released from actively contracting muscle and regulate coronary flow (58), but further evidence is required. Lidoflazine potentiates the coronary hemodynamic effects of adenosine, and may have an effect similar to dipyridamole (59). The data seem clear at present that dipyridamole has no

ameliorative effect on angina pectoris (60); however, comparable clinical data are not available for all of the agents under consideration here. Although preliminary clinical data have been encouraging, the capricious course of angina precludes rigid conclusions. Since none of these agents are known to increase the size of the coronary arteries, from coronary hemodynamic studies as they are now understood (40), it would not be predicted that they would be effective in relieving anginal pain.

Although aminophylline is widely considered to be a coronary vasodilator (61–63), hemodynamic studies in intact experimental animals and in man have failed to confirm this, at least insofar as measurement of coronary blood flow is concerned. Indeed, in the doses given, coronary blood flow increased only transiently (12, 64) or actually decreased in dogs (65) and in man (66). The xanthines are no longer considered helpful in treatment of atherosclerotic coronary artery disease.

Catecholamines and Sympathicomimetics

The coronary hemodynamic effects of catecholamines have been investigated by many different methods. There is agreement that catecholamines and sympathicomimetic drugs increase coronary blood flow (3). Thus, data indicate increased flow subsequent to the administration epinephrine (3), norepinephrine (3), isoproterenol (67, 68), DOPAmine (69), mephentermine (70), nylidrin (71), and atropine (72). The only problem in relation to these agents is whether the increase in coronary flow which they produce is conditioned by the metabolic response they elicit, or whether it is due to a primary effect on the vessels themselves. Some data suggest that epinephrine has a coronary vasoconstrictor effect followed by a myocardial metabolic effect producing coronary vasodilatation (3). From the point of view of the clinician and perhaps of the clinical pharmacologist, discussion as to whether these agents increase coronary flow through their metabolic or their vasodilator effects may appear to be academic; in any case, effects are so closely interwoven that clean separation is difficult if not impossible. Both effects appear within a few beats, and the myocardial circulation time is such that the delay in blood transit precludes knowledge as to which of the several cardiac cycles is included in specimens of arteriovenous blood analyzed for metabolic change. The problem cannot be studied effectively during ventricular fibrillation because the vigor of fibrillation is increased by epinephrine. Such potent measures are required to induce cardiac arrest that studies on the vessels during this state are difficult to interpret. Furthermore, the vigor of contraction increases very quickly with either catecholamine administration or sympathetic nerve stimulation, and any throttling effect of myocardial vascular compression must be weighed against actual contraction of the vessels themselves as a cause of decreased blood flow. There is the additional problem that the placement of a flowmeter about a coronary artery, although providing for accurate and continuous measurement of flow, disrupts some of the pericoronary nerves and may alter the response of

the myocardium to catecholamines. Indeed, pericoronary neurectomy increases coronary blood flow and decreases oxygen extraction (73). From the point of view of the purist, attacks on this Gordian Knot have obtained a result but, like the sword of Alexander, have not really solved the problem.

Recent data have indicated that β-adrenergic receptor blockade induced by propranolol produces a decrease in coronary blood flow (74). Again this has been accompanied by a decrease in cardiac output and cardiac dilatation so that the primary problem of vascular versus myocardial effect has not been clarified. The action of β-adrenergic blocking drugs has recently been reviewed (75). Both the systemic and coronary hemodynamic response to electrically simulated exercise has been reduced by β-adrenergic blockade (74) suggesting that this may explain why propranolol is effective in reducing anginal pain.

It has been reported recently that the hemodynamic effects of atropine are directly related to the increase in cardiac rate which accompany its administration (76). Surely the increased flow which occurs with atropine is consistent with a rate effect, since myocardial oxygen consumption increases and the coronary sinus oxygen content is unchanged (72).

Other "Biologic Products"

Other agents which may be found normally in the body may be considered as a group on the basis that they are produced spontaneously within the body. Of this group, vasopressin produces constriction of the coronary arteries as demonstrated by arteriography (6), and reduces coronary flow (77). In spite of the fact that it causes vasoconstriction, and reduces the oxygen consumption of the heart and the body as a whole, no evidence of myocardial hypoxia was indicated by cardiac lactate production. Although the systemic lactate levels rose considerably during vasopressin administration, the heart continued to metabolize lactate throughout the course of the study (77).

Synthetic angiotonin, administered to dogs, produced a significant rise in systemic arterial pressure and left ventricular work, accompanied by a considerable increase in left ventricular oxygen consumption. However, coronary blood flow was unchanged since coronary vascular resistance rose parallel to systemic vascular resistance (78). These data do not really bear on the question of whether angiotonin is a suitable agent to support arterial pressure in the presence of hypotension secondary to coronary artery disease with myocardial infarction, since the coronary response to raising blood pressure from a low level up to normal may well be different from that which occurs when blood pressure is raised from normal to a higher level. Furthermore, the response may be different in the normal and abnormal coronary vessel.

The systemic and coronary hemodynamic effects of thyroxin have been studied by observing its effects in experimental animals (79, 80), and in man as produced by thyrotoxicosis (81, 82). As might be expected, vasodilatation, increased metabolism, and increased blood flow occur in both the

systemic and coronary circulations. Successful treatment of thyrotoxicosis reverses each of these processes (81). Again, as with the catecholamines, it has not been possible to separate the metabolic from the vascular effects, since they are closely related. Studies of the effects of β-adrenergic blockade on cardiovascular hemodynamics in subjects with thyrotoxicosis have produced no evidence that catecholamines are important in the increased cardiac output, oxygen consumption, and cardiac rate (83). Similar data on coronary blood flow and myocardial metabolism do not seem to be available.

Bradykinin and related compounds have generally been found to increase systemic and coronary blood flow (84–86). The amount of increase in coronary flow was related inversely to the resting coronary flow. Thus, if the resting coronary flow was low, it tended to increase considerably, whereas if the resting flow was high, it tended to be unchanged or modestly decreased (85). The response was also modified to some extent by the degree of decrease which occurred in systemic arterial blood pressure, since if the blood pressure reduction was excessive, flow tended not to increase (85, 86).

Adenosine triphosphate and adenosine produce a marked increase in coronary blood flow as has already been indicated (55–57). Furthermore, adenosine may be the vasodilator that increases coronary blood flow in response to hypoxia. This idea is based on the fact that when an adenosine deaminase inhibitor is given during hypoxia, adenosine is recoverable from the coronary sinus effluent (87). The increases in coronary flow that have occurred subsequent to administration of adenosine and of adenosine triphosphate are much greater than those reported with most other compounds. From the rubor which develops in the myocardium, subsequent to their administration (57), it is suspected that the increased flow perfuses myocardial capillaries rather than shunting through arteriovenous anastomoses. Consequently, it seems likely that the predominant effect of these compounds is on the resistance vessels, i.e. the arterioles.

There has been considerable interest in the hemodynamic effects of several biologic amines, especially serotonin (5-hydroxytryptamine) since this agent is known to be released from platelets and appears surely to be released from argentaffinomas. Serotonin is a systemic and coronary vasodilator but does not produce pulmonary vasodilatation (88, 89). The mechanism of this action has not been clarified. An effective monoamine oxidase inhibitor, pheniprazine, has very little systemic or coronary hemodynamic effect (89) as does the monoamine oxidase inhibitor, pargyline (90). It is disappointing that these agents did not increase the hemodynamic effectiveness respectively of serotonin (89) and isoproterenol (68). These studies did not clarify the activity of monoamine oxidase inhibitors in reducing anginal pain and do not support the idea that they are effective through preventing the usual metabolic destruction of serotonin or isoproterenol. Monoamine oxidase inhibitors have been shown to decrease the cardiovascular response to exercise (91) and to affect the mood of many subjects. Both of these effects may be acceptable reasons for antianginal activity. It has been accepted since the time of John Hunter that angina may

be induced by emotion. Recent hemodynamic data from the intact awake dog have shown a profound increase in coronary blood flow in response to excitement (3, 92). This fact, coupled with long clinical observation, support the importance of psychosomatic aspects in treatment of subjects with coronary artery disease. No data are available concerning the effect of amine oxidase inhibitors on the reponse of the coronary circulation to emotion or excitement.

The endotoxin liberated from *Serratia marcescens* produced a hypotensive state similar to that of other endotoxins. This was accompanied by a decrease in coronary blood flow and cardiac efficiency associated with an increase in cardiac oxygen extraction (93). The state of shock produced was profound, and the hemodynamic effects reflect that state.

Hemodynamic Effects of Metabolites

Systemic administration of lactate increases body oxygen consumption (94, 95), as well as increases cardiac output (94), coronary blood flow and myocardial oxygen consumption (96). This effect may be due to its entry directly into the Kreb's cycle with direct stimulation of myocardial metabolism (97). Consequently, other members of the Kreb's cycle have been given to test whether they also might be active. Sodium succinate, administered in the same equimolar dose as sodium lactate, did not change the oxygen consumption, cardiac output, or coronary blood flow of dogs (98). Infusion of 50 per cent glucose was associated with an increase in cardiac output and a minor and insignificant increase in coronary flow (99). The changes with glucose were not at all comparable to those induced by lactate (96), and it seems probable that they were related to hemodilution and expansion of the blood volume (99). Thus, it would appear that the flooding of the body with metabolites which may enter the Kreb's cycle need not be associated with an increase in oxygen metabolism or direct coronary hemodynamic effects.

Sodium bicarbonate, on the other hand, produced marked changes in cardiac output and coronary blood flow, accompanied by rather striking decreases in peripheral and coronary vascular resistance (100). Both total body and myocardial oxygen consumption were considerably increased (100). It is seriously doubted that the effects of lactate or of bicarbonate are due to changes in pH, since rather gross increases in pH induced by hyperventilation

coronary flow in the dog and with a slight decrease in coronary flow in man (101). Similarly, administration of tromethamine (102) produced a considerable rise in pH with markedly increased venous carbon dioxide content, but no significant change occurred in cardiac output or coronary blood flow.

Antihypertensive-Diuretic Compounds

In general, administration of antihypertensive agents of the ganglion blocking group such as hexamethonium (103), trimethidinium (104),

trimethaphan camphorsulfonate (105), pentolinium (106), and mecamylamine (107) tend to be associated with a decrease in central venous pressure accompanied by a reduction in cardiac output and coronary blood flow. The mechanism of the reduced blood flow is presumed to be partially that of decreased venous return, since the reduced cardiac output is partially restored by supporting central venous pressure through transfusion and submersion in water (108). The possibility that decreased transmission of sympathetic impulses through peripheral sympathetic nerve endings (109), or through the ganglia, may also contribute to reduced cardiac output has not been excluded. Indeed, it is more credible as a result of the demonstration that β-adrenergic receptor blockade reduces cardiac output and coronary blood flow (74).

Contrary to this, both chlorothiazide (110) and triamterene (111) administration were associated with reduction in cardiac output, (110–114) but without significant changes in coronary blood flow (110, 111). These acute effects occur too early to be due to changed blood volume (110, 114), and are presumed to be a direct effect of thiazides on the vessels (115). This impression is strengthened by the observation that the very weak diuretic, diazoxide, a benzothiadiazine derivative, decreases systemic and coronary vascular resistance and lowers arterial blood pressure (116). Its administration produces an increase in cardiac output and coronary blood flow both in experimental animals and in man (116). More chronic administration of the thiazide drugs with sustained control of hypertension causes vascular resistance to fall (114), perhaps through effects on sodium distribution. Studies of coronary blood flow have not been made during this phase of the response to chronic thiazide administration.

Hydralazine administration, when it produced a reasonable decrease in systemic arterial blood pressure, also decreased systemic (117) and coronary vascular resistance (118). Both cardiac output and coronary blood flow increased and the coronary sinus oxygen content rose considerably. If the response to the agent was excessive hypotension, cardiac output did not rise (117). The latter response occurred only when the compound produced a shock-like state, and has little relevance to usual clinical administration of the drug. Guanethidine (119) and 1-(2-methoxyphenol)-4-(3-methoxypropyl)-piperazine phosphate (120) had similar results as far as the peripheral vessels are concerned. The latter of these compounds did not increase cardiac output or coronary blood flow (120). Although there is evidence that guanethidine releases catecholamines acutely (121–123), this is not solely responsible for peripheral vasodilatation since the same dilator response occurred subsequent to reserpine treatment (119).

Miscellaneous

Administration of salicylates in large doses was associated with considerable increase in oxygen consumption both of the heart (124) and of the body as a whole (124, 125); however, neither cardiac output nor coronary

flow changed significantly although both tended to rise (124). Others have found cardiac output to be increased by salicylate (126), and the difference between these studies is not clear although the anesthetics used were different. These effects would not seem to be due to pH changes but may well be related to the known activity of salicylates in uncoupling oxidative phosphorylation (127).

Administration of calcium chloride to intact anesthetized dogs was associated with a significant reduction in cardiac rate, cardiac output, and coronary blood flow, and by an increase in coronary vascular resistance (128). Simultaneous administration of atropine prevented the changes in cardiac rate suggesting that this may be a vagal effect, but information on the effects of atropine on coronary flow under these circumstances is not available. A recent report in intact awake dogs, using a different dose, showed that calcium administration increased coronary flow (129). This confirmed preceding experiments in the anesthetized open-chest dog (130, 131). Thus, it seems that the effect varies, probably depending on the rate of calcium administration and the preparation used or the degree of bradycardia induced.

Intravenous administration of chlorpromazine is frequently associated with a considerable decrease in systemic arterial pressure (132, 133). When administrated to anesthetized intact dogs, blood pressure decreases but significant changes do not occur in cardiac output or coronary flow (134). In isolated perfused rabbit hearts coronary flow increases, confirming its vasodilator effect in this preparation (135). Part of the decrease in systemic arterial pressure of intact dogs (134) was due to a decrease in cardiac output and part to a decrease in peripheral vascular resistance, but neither of these changes were of such magnitude as to be statistically significant.

The systemic and coronary hemodynamic effects of the antiarrhythmic agents, quinidine (136), and diphenylhydantoin (137) have also been studied. Quinidine, administered in a dose of 15 mg/kg to anesthetized mongrel dogs, produced an increase in cardiac rate accompanied by an increase in coronary blood flow and left ventricular oxygen consumption (136). Coronary vascular resistance was significantly reduced. Many of these effects may have been related to the increase in cardiac rate, since coronary flow and cardiac oxygen consumption are known to increase with cardiac rate (3, 31, 32, 138). Administration of diphenylhydantoin in a 5 mg/kg dose was associated with a decrease in cardiac output and cardiac work accompanied by reduced coronary flow and coronary vascular resistance (137). The changes in coronary flow and coronary vascular resistance were so variable that they did not reach statistical significance. In both of these experiments, large doses of the drugs were given. The chief justification for the dose chosen was that it reproduced the type of clinical response that the investigators wished to study. The fact that a larger dose is required in a healthy dog than in a diseased human being to produce a given response presents a philosophic dilemma that cannot be resolved

Conclusion

A great deal of information is available concerning the effects of various pharmacologic agents on the coronary circulation. Data accumulated by the nitrous oxide method in intact anesthetized dogs and in man appear to be comparable, and without significant interspecies variation. Available information has contributed considerably to our understanding of the clinical activity of cardiovascular drugs and has caused us to revise our concepts of the mechanism of action of many pharmacologic agents. Thus, although an agent that increases coronary flow and elevates the coronary sinus oxygen content would formerly have been predicted to be effective in relieving anginal pain in a subject with atherosclerotic coronary vascular disease, experience has shown that, commonly, it is not helpful. On the other hand, a drug which fails to increase the coronary sinus blood oxygen content, or to increase myocardial blood flow, would not have been predicted to be effective in relieving angina pectoris, yet experience has shown that such agents frequently are beneficial. Obviously, either the concept that effectiveness of drug of cardiovascular disease can be predicted from known hemodynamic effects is erroneous, or the wrong parameters have been selected for examination. One of the important factors in this study would appear to be change in major coronary artery size. Dilatation of the large coronary arteries on the surface of the heart may well be more important than dilatation of the resistance vessels which presumably control total coronary blood flow.

Our present understanding of coronary hemodynamics is related chiefly to the gross circulation rather than the microcirculation, and hence probably does not supply the information really required. Methods for studying distribution of blood flow within the myocardium are urgently needed.

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