Coronary Blood Flow in Relation to Angina Pectoris

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SUMMARY
The first portion of this paper represents a critical analysis of methods used in the determination of coronary blood flow in man. Coronary flow in man can be measured with the use of diffusible gases such as nitrous oxide, a procedure based on the Fick principle. In the presence of inhomogeneous perfusion, the time of equilibrium with coronary vein blood is difficult to establish, contributing to possible errors in the use of this method.

Procedures which utilize substances which actively enter the cell, such as $^{84}$rubidium, $^{86}$rubidium, $^{42}$potassium, and $^{34}$sodium, are also employed. Only when the blood-tissue permeability is great in comparison to blood flow, is the exchange between blood and tissue a flow-limited process and can be used as an estimate of the nutrient circulation. Since the technic is based on the assumption that there must be equality of integrated mixed venous and coronary sinus tracer concentration after injection until the measurements are complete, any inequality in the extraction ratio of the heart and the body may introduce an error. This is the case after acute myocardial infarction. The difficulties introduced by perfusion differential are even greater when washin and washout curves are obtained following the injection of $^{133}$xenon into the coronary artery.

Technics which determine flow by interpreting the slope of an exponential decay curve in the presence of underperfused areas must be interpreted with great caution in the presence of coronary artery disease. Measurements of total coronary sinus outflow by thermodilution or by indicator dilution suffer from possible inadequate mixing of blood with the injectate. They do not measure nutritional blood flow. The determination of phasic coronary flow with the ultrasonic Doppler flowmeter is promising, but the technic is invasive, and there are inherent difficulties in correct positioning of the catheter tip.

Determination of regional coronary flow is now also in clinical use. Usually gamma-emitting diffusible tracers such as $^{133}$xenon or $^{43}$potassium are used in addition to a scintillating camera and computers for data acquisition. Regional flow can be calculated with clearance formulae. Like other procedures used in the measurement of coronary flow, these methods suffer from the disadvantage that it is difficult to relate the rate of disappearance of the tracer substance to the degree of homogeneity of perfusion.

Subsequent portions of this report deal with changes in coronary flow in ischemic heart disease. As is to be expected, results are influenced by the technic used. This applies particularly to studies employing the xenon washout method. There is general agreement however that, in the presence of coronary artery disease, the coronary flow fails to respond adequately to coronary vasodilator drugs. An explanation may lie in the so-called "coronary steal": a decrease in resistance at the precapillary level of nonoccluded vessels could result in a decrease in blood flow to muscle supplied by that artery. The importance of coronary collateral circulation was described, and the development of collaterals from preformed thin-walled blood vessels was discussed. It is unlikely that the development of extensive coronary collaterals can prevent angina pectoris. Basic principles underlying coronary microcirculation, as they affect the oxygen supply of the heart muscle, were stressed. New findings relating to this subject are countercurrent flow and asymmetric capillary arrangement. This provides favorable oxygen distribution to the heart muscle. Of importance also is the existence of recruitment of capillaries (perfusion of the increased number of capillaries as perfusion pressure rises).

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Coronary collateral circulation Regional coronary blood flow

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IN 1809, the first textbook of cardiology written in English by Allan Burns appeared.1 In one of his chapters he clearly relates angina pectoris to coronary flow! "A heart, the coronary vessels of which are cartilaginous or ossified... can, like the limb, begirt with a moderately tight ligature, discharge its function so long as its action is moderate and quiet. Increase, however, the action of the body and, along with the rest, that of the heart, and you would soon see exemplified the truth of what has been said." Burns therefore described the causes of angina pectoris—the discrepancy between the coronary flow (the oxygen supply to the heart) and its oxygen demand.

Methods for Determination of Coronary Blood Flow in Man

An evaluation of methods used in man for the determination of coronary flow is necessary for the critical interpretation of data relating coronary flow to angina pectoris. In general, methods for measuring coronary blood flow in man can be divided into (1) methods using diffusible gases, (2) methods using diffusible substances or substances which actively enter the cell, (3) measurement of coronary sinus flow by continuous thermodilution, and (4) methods to measure phasic coronary flow by means of the ultrasonic Doppler flowmeter.2

Recently procedures have been introduced to measure coronary inflow by means of roentgen densitometry.3 The method is based on the indicator-dilution technic and on selective coronary arteriography. The technic is promising, especially since it can be carried out in conjunction with diagnostic studies, but it necessitates specially designed equipment and is an invasive procedure.

Unfortunately, electromagnetic flow transducers placed around the coronary arteries are not possible in man, except during cardiac surgery. It is believed by some that methods which do not directly determine coronary flow by means of electromagnetic flowmeters cannot be accurate and that the results obtained in the unanesthetized dog should represent the standard values for man as well. We agree with McGregor that "what we want to know is what changes we might find in patients with infarction, or angina, or shock, or after using drugs like nitroglycerin. We must ask ourselves the question, 'Can any of the methods used in man give us meaningful information about our patients and the mechanisms of anginal pain and the therapy we administer to them?"4 Most methods used for the determination of coronary flow in man have disadvantages, primarily those arising from the presence of coronary heart disease, which produce regions of inhomogeneous or differential perfusion.

Diffusible Gases

Diffusible gases can be used for the calculation of total flow based on the Fick principle using nitrous oxide as an indicator.5 The difficulty of the method is that it is necessary to know the time required for the tissues to reach equilibrium with venous blood. In the presence of inhomogeneous perfusion, the time of equilibrium with coronary vein blood is difficult to establish.

Diffusible Substances

Similar considerations also apply to the methods which utilize substances which actively enter the cell, such as 82rubidium, 86rubidium, 42potassium, and 24sodium. The factors which are involved in the exchange of these substances between the blood and tissues are the rate of capillary flow, capillary surface area, and permeability of the capillary and cell membrane.6 When the blood-tissue permeability is great in comparison to blood flow, the exchange between the blood and tissue is essentially a flow-limited process and can be used as an estimate of the nutrient circulation. This applies if permeability is not limited and constant clearance of the tracer is a function of the volume of capillary blood flow available for exchange. The technics which rely on the clearances of these substances by the heart are based on the principle of fractional distribution: there must be equality of integrated mixed venous and coronary sinus tracer concentration after the injection until the measurements are complete.7 The methods are, therefore, only valid if the extraction of the indicator by the heart is identical with that of the body. It is not essential that the extraction ratio of either the heart or the body be unity. What is important is that the ratio

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of rubidium extraction by the heart and by the body is equal during the time of observation. Hellberg and Rickart have demonstrated that under control conditions and after pacing to rates of 200 beats/min, the extractions of rubidium by the body and the heart are equal. However, after infusion of isoproterenol immediately following the production of an acute myocardial infarction, the extraction ratio or rubidium by the heart is considerably less than that of the body.

We have used $^{85}$rubidium, a positron emitter, combined with coincidence counting, in place of $^{86}$rubidium. This enables us to separate myocardial radioactivity from that of the surrounding tissue as well as from the activity of blood in the cardiac cavities.

Difficulties introduced by perfusion differential are even greater when washin or washout curves are obtained following the direct injection of $^{133}$Xenon into a coronary artery. This method makes it virtually impossible to detect small areas of underperfusion since resolution is inadequate to recognize these areas. The volume-flow ratio is frequently determined from the slope of an exponential, drawn through the first 50–60% of the decay of the indicator from its peak concentration. The presence of underperfused areas leads to exaggerated diminutions in coronary flow. Therefore, technics which depend on determining the slope of exponential decay to assess the rate of change of freely diffusible indicators should be interpreted with caution in the presence of suspected coronary artery disease. Some workers have avoided these pitfalls by using two indicators and by clarifying the influence of underperfused cardiac regions in patients by administering a constant infusion of indicator until a plateau was defined. This method, which is based on the calculation proposed by Zierler, necessitates catheterization of the orifice of a coronary artery and is therefore an invasive procedure.

**Continuous Thermodilution**

More applicable for use in humans are the measurements of total coronary sinus blood flow by continuous thermodilution or by indicator dilution. These procedures necessitate the use of specifically designed catheters placed in the coronary sinus. Adequate mixing of blood with the injectate is the fundamental assumption on which the accuracy of the method is based.

**Ultrasonic Doppler Flowmeter**

A promising new procedure, which has been introduced recently, measures total phasic coronary flow with an ultrasonic Doppler flowmeter. Piezoelectric crystals are placed at the end of a special catheter, which is connected to the Doppler ultrasonic flowmeter-telemetry system. The tip of the catheter must be placed at the ostium of the coronary artery. Phasic blood velocity can be measured, but the technic is invasive, and there are inherent difficulties in the correct positioning of the catheter tip.

In summary, procedures which determine nutrient coronary flow are influenced by the presence of underperfused cardiac muscle. Most promising are those noninvasive methods which utilize indicators which, during their passage through the heart, are actively taken up in the myocardium. However, capillary recruitment at increased flow rates may cause overestimation of flow, while reduced transit time may effect the opposite. The reason for this difficulty is that it is impossible with a single injection to distinguish the primary curve of the arterial concentration of the indicator from its recirculation.

**Coronary Flow in Ischemic Heart Disease**

It is likely that the disagreement on changes in coronary flow in ischemic heart disease results from deficiencies in technic, outlined above. One group of investigators believes that coronary blood flow is diminished in the presence of coronary artery disease. Others have found that coronary flow is increased in ischemic heart disease. When the xenon method was used to study the response of myocardial blood flow to tachycardia induced by pacing, there occurred a considerable increase in coronary flow during electrocardiographic changes and chest pain. This has been explained by assuming that either flow in the normal nonischemic area increases because noninjured muscle has to perform more work to compensate for the dysfunction of the ischemic area or that substances are liberated from the ischemic tissue, which produce vasodilatation in adjoining vessels. It is more likely, however, that the xenon washout method is unreliable in the presence of underperfused areas.

While there is little agreement on changes in coronary flow in the presence of angina pectoris and coronary artery disease, most
investigators agree that in the presence of coronary artery disease the coronary flow fails to respond adequately to coronary vasodilator drugs or to drugs which produce increased myocardial demands for oxygen.\textsuperscript{14, 18} This was demonstrated when it was shown that nitroglycerin increases coronary blood flow in normal individuals but has only a slight effect in patients with coronary artery disease.\textsuperscript{19} Knoebel and associates have used isoproterenol in the differentiation of abnormal and normal coronary circulation.\textsuperscript{14} Their results showed good correlation between the severity of coronary artery disease and the response of myocardial blood flow to increased demand. The explanation is not clear but may lie in dilatation of resistance vessels in the normally perfused area. This would shunt the blood away from underperfused regions. A decrease in resistance at the precapillary level of nonoccluded or normal vessels could result in a decrease in blood flow to muscle supplied by that artery through collaterals—a "coronary steal" syndrome.

The term "coronary steal" was originally introduced by Effler and associates in connection with the retrograde flow recorded in left anomalous coronary arteries arising from a pulmonary artery.\textsuperscript{20} The idea was expanded by McGregor, who, in comparing the action of two coronary vasodilators, nitroglycerin and dipyridamole, found that the latter drug significantly reduced retrograde flow and peripheral coronary pressure, despite a greater fall in mean arterial pressure.\textsuperscript{21} They interpreted this difference by assuming that in the case of dipyridamole, small arteriolar resistance vessels dilate; with nitroglycerin, on the other hand, primarily dilatation of the larger conductive vessels occurs. Thus, dipyridamole "steals" from the ischemic area by causing vasodilation of the resistance vessels in the nonischemic areas, while nitroglycerin, in dilating the conductive vessels, shunts blood through collaterals to the ischemic areas.\textsuperscript{21} Therefore, some coronary vasodilators may actually precipitate angina pectoris even though they are known to increase total coronary flow.\textsuperscript{22} Whether the phenomenon of coronary steal plays a significant role in the production of angina is as yet not clear.

**Coronary Collateral Circulation**

The existence of a network of fine vessels connecting the coronary arterial tree has been recognized for many years. It has been thought that, because the pressure in the major coronary artery distal to the ligature was only 30 mm Hg, adequate perfusion through these collaterals was not possible. More recently, Coulson and Grayson measured the pressure in the small arterial anastomotic branches of the coronary vascular network and found it to be not different from the mean values for peripheral coronary pressure measured distal to a ligature on the anterior descending branch of the left coronary artery.\textsuperscript{23} They found that the coronary capillary circulation must have both capacity and compliance, and that distensibility (or compliance) accounts for filling of the network during the systolic phase of coronary flow.

Schaper has examined the rate of growth of a collateral from a preexisting thin-walled vessel and its transition to a small artery.\textsuperscript{24, 25} He and his co-workers have demonstrated that, following placement of an ameroid constrictor around the circumflex coronary artery in dogs, the vascular diameter increases rapidly.

By means of electron microscopy, Schaper and associates have observed the fine structural details in developing coronary collaterals after occlusion of the circumflex branch.\textsuperscript{25} Sustained maximal vasodilation to which these small vessels are exposed, because of the marked increase in tangential wall stress, apparently results in cellular hyperactivity in the endothelium as well as in the medial smooth muscle. The capacity of this reaction however is soon exhausted, and endothelial cells begin to degenerate. At this stage, vascular permeability increases and endothelial gaps may allow the passage of bloodborne
cells into the vessel wall. At about 8 weeks, there is subendothelial proliferation; and after 1 year there is less extracellular material, and the general picture of regularity prevails.

Much has been learned about the development of coronary collaterals. However, it is likely that even in the presence of extensive collateral circulation angina pectoris can occur. This is not surprising, since there is no agreement on the relationship between the degree and location of coronary stenosis and the severity of angina. It has been found that even the distribution of coronary arterial obstruction, shown by selective cinecoronary arteriography, is of little value in relation to the pattern of angina pectoris. Division of patients with angina into groups on the basis of duration of symptoms also could clarify the natural history of symptomatic obstructive coronary artery disease. The difficulty in the interpretation of these results is our inability to relate quantitatively the collateral flow to the degree of angina.

**Coronary Microcirculation**

What role can alterations in coronary microcirculation play in the supply of oxygen to the myocardium and the mechanism of angina?

For technical reasons few studies on the coronary microcirculation have appeared in the literature. This is primarily because adequate illumination of the field of study has been difficult. Epillumination furnishes the best means of visualizing the coronary microcirculation, but very clear pictures of interfibrillar capillaries with good resolution are, as yet, not available. For this reason, we have developed a method which relies on transillumination of the left atrial muscle of the cat—a thin muscular structure. This was accomplished by inserting a light-conducting single fiberoptic rod, which transmits light from a pulsating xenon arc through the left atrial muscle of the cat. This results in transillumination of a specific area. Using color films at 400 frames/sec, we were in a position to obtain pictures of movements of individual red cells in capillaries during both phases of the cardiac cycle with a total magnification of the film of 32 times.

Certain characteristic features of the coronary microcirculation have emerged, which may have some bearing on the oxygen supply of the myocardium. For instance, the presence of countercurrents and asymmetric capillary arrangement is of importance for the oxygenation of the heart muscle. Countercurrents—that is, opposite flow in capillaries lying on either side of a muscle fiber—were frequently noted, particularly in the presence of interconnecting capillary loops. The importance of this pattern for the oxygenation of heart muscle was previously stressed by Luebbers and associates. In adjacent overlying plains of muscle, there was a multiple sheet arrangement of capillaries with vessels connecting the layers. This asymmetric arrangement with occasional countercurrents casts doubt on the validity of the Krogh-Erlang equation, which defines the transfer of oxygen from capillaries to the surrounding tissue. This equation assumes the presence of cylindrical symmetric arrangement of capillaries with parallel unidirectional blood flow, which appears not to be valid on the basis of our findings. Capillary recruitment also plays an important role in the oxygenation of cardiac tissue.

When the perfusion pressure is raised in the perfused arrested heart, the number of capillaries with discernible red cell movement increases (recruitment). However, with recruitment red cell velocity in individual capillaries usually remains constant. With nitroglycerin, perfusion pressure diminishes, but red cell velocity also remains unchanged. Constant capillary red cell velocity, in the face of changing perfusion pressure, denotes an intrinsic tendency of the coronary microcirculation to maintain constant flow. We refer to this as “capillary autoregulation,” although it is in all likelihood the smooth muscle of the precapillaries which is responsible for this phenomenon.
We have observed that the two phenomena, capillary autoregulation and recruitment, occur simultaneously in the coronary microcirculation under the influence of nicotine. In this instance, a rise in perfusion pressure results in an increase in the number of perfused capillaries, while red cell velocity remains constant.

What is the importance of these findings for the mechanism of angina pectoris? The anatomic pattern of the coronary microcirculation is fixed, and, as we have seen, sufficient tissue oxygenation is maintained by asymmetric capillary distribution (countercurrents, asymmetric capillary arrangement, and multiple sheet arrangements). Autoregulation also contributes to the maintenance of adequate red cell velocity. Since the capillaries are devoid of smooth muscle, they cannot by themselves, through intrinsic mechanisms, alter capillary flow or capillary resistance. If, therefore, capillary perfusion should contribute to insufficient oxygenation of the heart muscle, it must be the result of alterations in pressure and resistance primarily proximal to the capillaries, where pressure and resistances can be altered. However, autoregulation and recruitment, or asymmetric flow, are means which safeguard an adequate oxygen supply on the capillary level.

**Angina and Regional Coronary Blood Flow**

The anatomic changes found on coronary cinematography or at autopsy demonstrate that characteristically in hearts involved with coronary artery disease blood flow is nonuniform, with patchy areas of poor perfusion. Angina originating from these regions may be the result of a discrepancy between perfused and nonperfused areas.

Several procedures for the determination of regional coronary blood flow have been attempted, and some of them are in clinical use. All of them, with the exception of those carried out on the exposed heart, suffer from the disadvantage that it is difficult to relate the rate of disappearance of the tracer substance to the degree of homogeneity of perfusion. Most of these use procedures with radioisotopes, such as xenon clearances.

Maseri and associates have developed a method of regional dynamic study of myocardial blood flow in man using a gamma-emitting diffusible tracer such as $^{133}$Xenon, in addition to a scintillation camera and computers for data acquisition and processing. By these means, they are able to determine the washout curve from a single zone of the myocardium selected from the scintigram. The radioactive tracer is injected directly into a coronary artery. For the selected areas, the time/activity curve can be obtained and plotted or printed out simultaneously. The data acquired can be processed and then stored in a computer digital tape unit. Regional flows are calculated with the usual clearance formula.

MacIntyre and his group used $^{40}$potassium and scintillation cameras. The accumulation of the radioactive material in the myocardium was determined by collecting similar distribution matrices every minute and delineating the area that can be identified on the scan on the heart border. Since they used Sapirstein's principle of fractional distribution, the whole-body clearance of the radiopotassium from the circulating blood must also be determined. Reasonable agreement has been achieved between estimation of the fraction of dose in the myocardium in vivo and the measurement of the myocardial uptake in the excised heart. The method is based on that described by Leb and by Goldschlager and associates.

The technic of Maseri suffers from difficulties in interpreting the disappearance curves of clearance from the heart muscle, and that of MacIntyre suffers from the assumption that there is equality of integrated mixed venous blood and blood draining from the underperfused region. These approaches, however, are promising for relating regional perfusion to angina.

Horwitz has recently measured the effect of nitroglycerin on regional myocardial blood
flow in patients with coronary artery disease using the regional clearance of \(^{133}\)Xenon.\(^{35}\) The isotope was injected directly into the myocardium. Tracings were obtained prior to and 5 min following the ingestion of nitroglycerin.

Two exponential decay curves were found—an early rapid and a slow terminal clearance. Nitroglycerin resulted in an increase in the fast flow, and the slow-flow component also was elevated in the majority of patients. This procedure, which has the advantage of being able to visualize and to measure directly the perfusion of localized areas of the heart muscle, has the disadvantage of all clearance methods: that the volume/flow ratio is determined from the slopes of exponential curves drawn through various portions of the decay of the indicator. However, by injecting the isotope directly into a specific region of the myocardium, one limits the difficulty of analyzing curves which are the composite of unequal perfusion. Unfortunately, this technic is limited to the occasions when the myocardium is exposed.

Conclusions

The discussion has stressed the major factors which influence coronary blood flow in man and thus angina pectoris. A critical analysis of measurements of coronary blood flow in man was presented. It was concluded that most methods used to measure nutritional blood flow in man are influenced by the presence of underperfused cardiac muscle. Most promising are the noninvasive methods which utilize indicators, which during their passage through the heart are actively taken up by the myocardium. However, these procedures also are influenced by increased flow rates or underperfusion.

There is no general agreement in the changes in coronary blood flow in angina pectoris and in ischemic heart disease. However, evidence suggests a diminution rather than an increase. In patients with coronary artery disease, coronary flow fails to respond adequately to vasodilator drugs or to drugs which produce increased myocardial demands for oxygen. This may be the result of flow deprivation of portions of the heart muscle supplied by stenosed arteries and collaterals—a phenomenon referred to as “coronary steal syndrome.” It is possible that this is responsible for the difference of action of coronary vasodilator drugs such as dipyridamole and nitroglycerin.

The importance of coronary collateral circulation was discussed, and concepts were presented which dealt with pressure and flow in these vessels. The formation of large collateral arteries from thin-walled arterioles was described. Although collaterals transform end arteries into a network of anastomosing vessels, the effect of collaterals on the prevention of angina pectoris remains uncertain.

Studies on the coronary microcirculation reveal asymmetric capillary arrangement and capillary countercurrents. These factors are of importance for the oxygenation of the heart muscle. Capillary autoregulation and recruitment of capillaries may furnish safeguards against regional ischemia.

The possible importance of nonuniformity of coronary flow in the etiology of angina was stressed, and methods for the measurement of regional coronary flow were described.

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