The Functional Importance of Coronary Collaterals

By Carl J. Wiggers, M.D., Sc.D.

The physician attending a patient with a recent coronary occlusion is confronted with many questions of prognostic importance: How long will muscles in the ischemic area remain viable? What will determine the size, shape, and depth of the infarct? What are the chances that collateral blood supply will limit its extent, promote healing, and prevent subsequent aneurysmal dilatation? Are drugs likely to be helpful? Careful clinical observations followed by necropsy control can suggest answers to these questions; basic knowledge derived from experimental studies helps to establish the correctness of the answers.

ANATOMIC ASPECTS

The blood supply of mammalian hearts is derived from two coronary arteries arising from the root of the aorta. The left divides almost immediately into the left circumflex and the anterior descending rami. The former runs in the A-V groove to the left, reaches the posterior aspect of the left ventricle, and terminates in a posterior descending branch. The ramus descendens anterior circles left to the pulmonary artery and then runs downward in the interventricular groove toward the apex. Near its origin it gives off septal branches to the septum. The right coronary artery runs to the right in the A-V groove and terminates posteriorly in several descending branches on the right ventricle. Special twigs, variable in origin, supply the sinus nodal tissue. These are indicated in a composite drawing of figure 1.

Branches of the several main coronary arteries pass superficially in the general direction of the apex. They divide into intramural branches which course directly into the ventricular muscle. At the apex, coronary branches turn inward with muscle bundles to supply the inner layers of both ventricles and the papillary muscles. Anatomic studies have revealed that the branching of vessels within the myocardium is related to muscle bundles, but numerous intercommunications exist between vessels of different bundles.

In the dog's heart, the left atrium and ventricle are supplied largely by the two left coronaries, and the right ventricle by the right circumflex, but communications of arteriolar size or larger exist in superficial layers between territories supplied by the three principal coronary arteries. It should be noted that such collateral communications are apparently absent in the deeper layers.

In the human heart the distribution appears to be more variable. According to studies of Schlesinger, three general patterns of distribution can be recognized: (a) right coronary preponderance, (b) left coronary preponderance, and (c) a balanced distribution. However, Schlesinger and his associates were not able to demonstrate significant intercommunications between these systems in normal human hearts.

In addition to the aforementioned intercoronary communications, connections of intramural branches with the ventricular cavities...
and extracoronary vessels have also been demonstrated.

**Hydraulic Principles**

The demonstrations that anastomotic channels exist does not prove that they carry blood under normal or pathologic conditions. Flow of blood from one main vessel to tributaries of another through communicating channels requires a pressure difference, the magnitude of which depends on the resistance offered by the communicating tubes.

Let us examine the facts upon which predictions can be made of the probability that blood flow can be established through these various channels. During diastole the mean pressure in an occluded coronary artery is approximately 18 mm. higher than in the left ventricular cavity. Consequently, if any flow occurs it would therefore be from the coronary vessels to the ventricular chamber. During systole the mean pressure in the left ventricle exceeds that in an occluded coronary artery by about 45 mm., but the connections between the ventricular cavity and coronary arteries are compressed by myocardial contraction. It is therefore dynamically inconceivable that any material volume of blood could be transferred from the ventricular cavity even if communications of very large caliber were present. Experimental studies have corroborated such inferences: when the three principal coronary vessels are temporarily occluded, no blood flows from the peripheral ends of coronary vessels.

On the other hand, when a coronary artery is ligated, a mean pressure differential of approximately 66 mm. Hg exists between other branches of the aorta and the occluded vessel throughout the heart cycle. Since these communicating channels are not compressed during diastole, a flow during this phase would be dependent largely on the diameter, length, and number of such communications. It would also be determined by the duration of each diastole or, in other words, the heart rate. Since such collaterals are apparently developed better in hearts of dogs than in those of man, it may confidently be expected that the dog is a favorable animal for demonstrating their functional importance.

**Experimental Evidence**

For a number of years the present writer and his colleagues hopefully pursued experimental studies to demonstrate the existence of functional collaterals in the normal dog's heart, but without success. The most conclusive evidence that collateral flow is inadequate in the normal dog's heart was (a) the demonstration of Tennant and the writer that ligation of the main coronary artery causes the ischemic area to stretch rather than to shorten during systole, and (b) the further observation with Green that this cannot be prevented or abolished by drugs which elevate arterial pressure or have an alleged dilating effect on coronary vessels. Apparently, intercoronary communications are too small in relation to the pressure differentials which exist during diastole to transfer adequate quantities of blood. In short, in normal hearts of dogs the coronaries are functionally, though perhaps not anatomically, end arteries.

With this view the recent investigations of Prinzmetal and his group are apparently in disagreement. They maintain that collaterals of significant size exist in normal hearts of animals and man which serve a physiologically useful purpose. The evidence which they sub-

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**Fig. 1.** Composite diagram illustrating the variable origins of arterial supply for the sinus node.
mit in favor of this view therefore deserves the most careful evaluation. The following serves as a brief summary of their various procedures and comments with respect to interpretations:

Procedure I. Human hearts obtained at necropsy were perfused through both coronaries with kerosene under equal pressures. Clamping of one coronary increased the flow through the other by approximately 1 per cent. Such results cannot be applied to the beating heart in situ, for the pressures used exceeded the differential pressures which can develop; the viscosity of the perfusion fluid was lower than that of the blood, and the vessels were neither compressed during systole nor under myocardial tension during diastole. Various types of experiments on the beating heart in situ in our laboratory have shown that clamping the right coronary artery has highly variable effects on left coronary flow, probably owing to alterations in cardiovascular dynamics. Also, although the flow of blood from the peripheral end of a severed coronary artery gradually increases after ligation of its main branch, it is never of sufficient magnitude conceivably to nourish the ischemic area.

Procedure II. When the left coronary artery was perfused with tiny glass spherules suspended in a radiopaque medium, those ranging between 70 and 180 microns apparently passed through vessels of arteriolar size to branches of the right coronary artery. Similarly, spherules 70 to 120 microns entered the ventricular cavities presumably through arterioluminal channels. Some beads of even larger size were recovered from the coronary sinus, suggesting the presence of arteriovenous shunts.

Since it is dynamically impossible for any consequential flow to be derived from the ventricular cavities in the beating heart, the passage of spherules of large size in the dead heart obviously does not furnish evidence as to sources of blood supply to a potentially infarcted region. It is also possible to overestimate the vascular caliber from the size of beads which pass. One can, for example, force marbles through an elastic rubber tube of much smaller diameter than that of the marbles themselves. Since the perfusion pressures used exceeded the possible differential pressures in the beating heart, and since the vessels might have become more expansible as a result of the incubation process which preceded injection, such a possibility cannot be excluded.

Procedure III. Human hearts similarly pre-treated were perfused via a left coronary ramus with red cells rendered radioactive by incubation with P32. A pressure of 100 mm. Hg was used for such perfusion. The ventricles were unrolled and placed on a flat surface, and the radioactivity of different regions was determined by a Geiger counter. The results apparently demonstrated that the epicardial regions of the right ventricle contain nearly as much radioactivity as the left ventricle.

Assuming that hemolysis and the post-mortem diffusion of P32 from red cells were adequately controlled, the question as to a similar occurrence in the beating heart obviously required further investigation. The Los Angeles group were fully cognizant of this and therefore turned to the study of beating hearts.

Procedure IV. Radioactive erythrocytes were injected intravenously into moribund patients having coronary infarcts. Geiger counts of the hearts obtained post mortem revealed a high degree of radioactivity in the infarcted areas. These tests were supplemented by experiments on dogs: radioactive erythrocytes were similarly injected intravenously after ligation of the ramus descendens anterior. The heart was frozen rapidly and unrolled. Geiger counts and radioautographs again demonstrated nearly as marked radioactivity in the epicardial layers of the area supplied by the occluded ramus as in other regions of the ventricles, but the endocardial layers of this region exhibited significantly less radioactivity.

It is a common experience in research that experimental results which seem crucial at the moment turn out to be inadequate with aging. The apparently obvious conclusions regarding the efficiency of coronary collaterals which are suggested by these brilliant experiments must, however, be squared with other observations made at the same time. The Los Angeles investigators, as many others before them, noted that the ischemic area becomes cyanotic and that infarction generally follows in dogs which
survive. Hence the presence of radioactive red cells in an ischemic area could not have signified that the blood supply approached that of the normal myocardium.

The volume of blood found in a tissue after death is not a criterion of blood flow during life. It is extremely difficult to differentiate between blood in active circulation and that which may have stagnated, in the sense that the process of stagnation does not necessarily involve complete immobilization of corpuscles, but a slow onward displacement. Indeed, periodic expansion of an ischemic area alone might cause a slow forward movement of corpuscles. In such an event the rate of flow would necessarily be small, the oxygen consumption would be more complete (cyanosis), but the oxygen supply per minute would be wholly inadequate. Such a situation obviously explains the evidences cited in support of a different interpretation, namely that an active flow is demonstrated. Finally, Blumgart and his associates have recently pointed out the difficulty of being certain of “the amount of radiation contributed respectively by blood in surface veins, possible capillary extravasations incurred in infarction and rapid freezing, and the diffusibility of P\textsuperscript{32} from red cells into plasma even during short periods of time, particularly if hemolysis has occurred.”

Summarizing, the distribution of radioactivity determined post mortem offers no crucial evidence for the existence of an adequate blood flow to a region deprived of its main coronary supply; whereas the cyanotic appearance is clear evidence of failure of a functionally useful blood flow.

Procedure V. Fluorescein injected intravenously in dogs after ligation of the ramus descendens was shown by the aid of cinematographic color photography to appear promptly in the margins of the involved area and to spread concentrically to its very center approximately in 16 seconds. Striking as such visual tests are, they give no information as to the magnitude of the collateral blood supply, or indeed as to whether spread of the highly diffusible dye occurred via blood vessels or lymphatic channels. It has been our experience that any dye similarly injected tends to remain localized permanently; it does not fade on recirculation of diluted dye. It was also noted by Prinzmetal and his group that the fluorescein coloration did not penetrate to the inner layers of the myocardium, but was limited to the outer third of the wall. This confirms the general opinion that collateral circulations such as exist are limited to superficial regions of the myocardium. Therefore, if their observations denote an adequate blood supply, it may be expected that the superficial layers of muscle will retain their viability at the time that the dye reaches this area. As already mentioned, myographic records of such surface fibers have demonstrated over and over again that, by the time the fluorescein was found to color the whole area (about 16 seconds), the muscle begins to stretch instead of shorten during systole. These composite observations would indicate that coloration of an area is not a good criterion of an adequate blood supply.

Procedure VI. The Los Angeles investigators, however, claim to have demonstrated by use of rapid motion pictures and measurement of ventricular borders in successive frames that bulging of the affected area may disappear or wax and wane; “the noncontractile myocardium regained its contractility a few seconds later.” This was attributed to periodic variations in collateral blood supply. The present author and his many associates have recorded optical myograms following occlusion in hundreds of experiments and have never witnessed such a phenomenon, nor are such contractions reestablished after a coronary artery has been occluded for more than 20 to 60 minutes. It has been suggested elsewhere that these differing observations may be due to the fact that changes in the borders of the ventricles recorded cinematographically or otherwise represent composite effects of changes in position and volumes of the ventricles, and therefore cannot equal the accuracy of myograms which, when properly applied in the direction of surface fibers, accurately record the distance between two points.

Therefore, the results obtained by Prinzmetal and his group through employment of new and ingenious technics have not altered our opinion
that in normal dogs the collateral supply of the surface layers is not adequate to maintain contractions of sufficient force to prevent the ventricular wall from stretching in the affected region. As a corollary, it is highly improbable that any better functional supply could develop in human hearts which have demonstrably poorer collateral channels.

**The Development of Collaterals**

Abundant evidence exists that the potential intercoronary and extracoronary communications present in normal hearts can develop into functioning channels when a main branch is *slowly* occluded. The morphologic evidences are (1) that large intercoronary communications have been found post mortem in human hearts exhibiting sclerotic changes in one or more main branches, (2) that occasional instances have been reported in which complete occlusion of coronary arteries without infarction was seen, and (3) that pigs, which have no anatomically demonstrable vessels such as dogs, develop collaterals after chronic reduction in blood supply. The experimental evidence that intercoronary communications enlarge include the following observations: (4) When a main coronary branch is slowly occluded in dogs by mechanical clamps, cellophane bands, or osmotic devices, the retrograde flow from a peripheral end increases significantly over the normal, which is only a few drops per minute. The peripheral pressure also increases and the recorded pressure pulses may display earmarks of directly transmitted arterial pressures. (5) Temporary increase in aortic pressure in such preparations greatly accentuates such retrograde flow and pressure, whereas temporary clamping of other coronary arteries abruptly decreases or completely stops retrograde flow. (6) Myographic records taken from an area of slow occlusion in dogs which survive indicate that the region is undergoing shortening and that the newly developed collaterals are functioning in adequate fashion. Very occasionally—perhaps in animals which have developed sclerotic changes previous to ligation—this has also been found in chronic dogs that survive complete ligation. Such observations must be kept in mind in evaluating results of surgical procedures designed to revascularize the heart.

The interesting and hopeful clinical deduction may perhaps be drawn that progressive development of coronary sclerosis which primarily operates to throttle coronary flow may provide a natural mechanism leading to development of collaterals sufficient to mitigate or prevent infarction when a main vessel is subsequently occluded.

The factors which determine the development of such collaterals are not covered by the assertion that collateral circuits develop in ischemic regions owing to the need for more blood. The present writer has suggested that the slow establishment of differential pressure gradients following partial or complete occlusion of a main branch distends normally useless vessels to such a degree that they become pervious. This may be aided by their active dilation through development of a state of anoxia, which has been demonstrated to be the most powerful coronary vasodilator known.

**The Effect of Drugs**

It is naturally of clinical interest to inquire whether it may be anticipated that flow through collateral channels can be augmented by use of drugs demonstrated to have a vasodilator action. This includes the nitrites, xanthines, papaverine, and adenylic compounds. The nitrites should obviously not be administered in doses sufficient to reduce arterial pressure, particularly if this is already low. There is no substantial experimental evidence that alcohol, which is a potent dilator of cutaneous vessels, has a similar effect on the coronaries. In fact, the accumulation of blood in the skin may lead to a diminution in venous return and so reduce cardiac output and arterial pressures further. Coronary vasodilators might conceivably exert a favorable action (a) by increasing the caliber of potential communicating channels, (b) by reducing an alleged constriction of patent coronary vessels that supply the collaterals, or (c) by a passive dilation through elevation of arterial pressure in the event that marked hypotension exists.
The most critical experiments offer no support for the belief that any drug can penetrate connecting collaterals in normal hearts. None of the drugs investigated in our laboratory were able to abrogate or diminish the expansion of an ischemic area. Some observers, it is true, believe that the size of infarcts is reduced through their use; but such comparisons are necessarily made on different animals and must rely on measurements which do not include depth and are therefore hazardous owing to the variability of the infarcted area in dogs. Also in interpreting the effects of coronary vasodilators on surface infarctions a distinction should perhaps be made between effects due to opening of collaterals and those which are secondary to overlapping blood supplies. In dogs the margins of areas supplied by the three principal coronaries normally receive a dual blood supply. When a main coronary is constricted these margins naturally escape ischemia. By dilating the direct branches of the vessel which remains patent the blood supply may conceivably be somewhat extended.

The concept that intercoronary reflexes cause a constriction of other coronary vessels could not be confirmed in our laboratory and there appears to be no value in the use of drugs on such a basis. Pressor amines, such as epinephrine, norepinephrine, ephedrine, Norepinephrine, and others, have been advocated on the grounds that elevation of the pressure head plus dilatation of subsidiary coronary circuits should act favorably in forcing blood through collaterals. This is especially advocated in cases showing a low arterial pressure. Great circumpection should be used in the employment of such agents owing to certain counterindications. All of them increase the work of the heart, elevate pulmonary pressures, and tend to induce ventricular arrhythmias. In addition, epinephrine causes a deterioration of energy stores in cardiac muscle which would seem to be highly undesirable. Since the best experimental evidence indicates that the decline of arterial pressure following coronary occlusion is most probably due to failure of muscle which is still viable to compensate for the loss of contraction in ischemic areas, the use of cardiac stimulants, such as those of the digitalis series, would seem to be more plausible. Unfortunately, owing to the slow action of these agents, their effect on the caliber of coronary vessels has not yet been demonstrated satisfactorily in experimental animals.

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CARL J. WIGGERS

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