CLINICAL PROGRESS

Current Research and Problems of the Coronary Circulation

By Donald E. Gregg, Ph.D., M.D., and David C. Sabiston, Jr., M.D.

Heart disease, especially coronary artery disease, continues to be one of the foremost problems in medicine today. A good estimate is that about one third of those who die from heart disease in the United States do so from a primary coronary insufficiency related to atherosclerosis as the dominant factor, one third die from primary coronary insufficiency associated with cardiac hypertrophy and increased cardiac work arising from valvular lesions and increased blood pressure, and one third as a result of a primary myocardial insufficiency.

Of the available methods of study, none gives detailed or accurate information regarding the coronary system in the normal or diseased state. Such studies require precise methodology that is difficult to apply to the heart because of its gross inaccessibility. For this reason various types of instrumentation are introduced in order to obtain hemodynamic and metabolic data, but such data are often of doubtful value. Accordingly, advances in the field of the coronary circulation are based on a combination of difficult precision instrumentation applied directly to the exposed or isolated heart and of questionable indirect methodology applied to the heart in the intact state. By synthesis of available experimental facts, however, considerable progress has been made toward the solution of certain problems in this field.

Metabolic Patterns in the Heart. Since the ability of the heart to do work depends basically on its biochemical activity leading to muscular contraction, any definitive analysis of the phenomena of heart failure or coronary insufficiency is dependent upon an understanding of the normal metabolism of cardiac muscle. Basic chemical patterns in cardiac muscle have been found similar to those in other muscles and tissues. The catabolism of fat, carbohydrate, and protein produces free energy, about half of which is dissipated as heat and half is captured as phosphate bond energy. The latter is used for muscle cell work and for various anabolic activities such as synthesis of glycogen, lipids, proteins, and enzymes. These catabolic and anabolic reactions proceed simultaneously under the influence of a complex system of enzymes, coenzymes (from the vitamin B complex), and hormones. Compounds such as adenylic acid and creatine accept the high energy phosphate moieties from the oxidation of substrate to form phosphocreatine and adenosine triphosphate. It is believed that the ultimate contractile unit in muscle tissue is the actomyosin fibril, a conjugate of two muscle proteins, polymerized actin and myosin. Conversion of actin into polymerized actin requires energy that is transferred from nucleotides such as adenosine triphosphate and is released enzymatically, presumably during ventricular diastolic relaxation, so that shortening of the muscle fibril can take place during the next systole. Up to the present time biochemists have appeared to be interested primarily in adenosine triphosphate as the chief nucleotide furnishing the energy for contraction. However, recent work in at least two laboratories has shown that the content of adenosine triphosphate and adenosine diphosphate is the same in the resting and the beating heart. This raises the question of whether or not adenosine triphosphate is the

From the Department of Cardiorespiratory Diseases, Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington 12, D. C.
main donor of phosphate bond energy and indicates that a new revolution in the physiology of muscular contraction may have begun. Coronary catheterization studies in dog and man have indicated that the heart can choose its fuel from a variety of foodstuffs. Thus, it is largely independent of fluctuations in its chemical environment. To determine the quantitative contribution of fat, carbohydrate, and protein to the energy production of the heart, i.e., its oxygen consumption, measurements have been made of their cardiac extraction (coronary artery — coronary sinus difference), their total uptake (coronary flow × (coronary artery — coronary sinus difference of substance]), and the myocardial respiratory quotient (coronary sinus — arterial carbon dioxide difference)/(coronary artery — coronary sinus oxygen difference). In general, the myocardium of the normal left atrium and ventricle has been found to extract oxygen, glucose, lactic and pyruvic acids, fatty acids, ketone bodies, and amino acids in direct relation to the arterial level of each substance. Excellent correlation has been demonstrated between the myocardial respiratory quotient and the myocardial uptake of a substance. During fasting, the heart can derive its energy from fat as indicated by a myocardial respiratory quotient of 0.7 with a very low extraction and uptake of carbohydrate. In the normal postprandial state, the metabolism of the heart may be based largely on carbohydrate, since its respiratory quotient approximates 0.9, with a high extraction and uptake of carbohydrate and with a negligible uptake of amino acids. Even the substitution of 5 to 10 per cent oxygen for the normal 21 per cent in the inspired air does little to change carbohydrate uptake by the normal heart.

In addition to these patterns of myocardial metabolism in the normal heart, other metabolic changes have been reported in some pathologic and diseased states. Patients with heart failure and decreased cardiac work due to valvular disease show an increased carbohydrate uptake by the heart with a normal extraction of lactate and pyruvate and an increased glucose extraction. The heart in the patient with even mild diabetes appears to derive most of its energy from fat, with a postabsorptive respiratory quotient of about 0.7, an increased uptake of fatty acids, and a decreased carbohydrate uptake. It is well to defer detailed consideration of much additional metabolic data that have been reported in other states, because an interpretation must be based on the assumption that oxidation of foodstuffs to carbon dioxide and water is the sole factor in the determination of the myocardial respiratory quotient and of the myocardial extraction and uptake of these compounds including oxygen. Without doubt, storage or conversion into other compounds is occurring concurrently and these activities are especially prominent during changing levels of cardiac activity or of blood substrate.

Basic Regulation and Concepts of Coronary Circulation. In any consideration of the problems of the coronary circulation, certain basic concepts are essential. Beginning with Harvey in the seventeenth century, the anatomic and dynamic details of this system have been elucidated gradually (fig. 1). As in any other vascular system, each of the two coronary arteries that arise from the aorta connects with its capillary bed, its superficial myocardial venous bed, and eventually with the right atrium. The epicardial branches of the coronary arteries and coronary veins also anastomose with each other and with extracardiac arteries and veins. There are numerous
arteriovenous shunts. In addition to these pathways, the arterioles as well as the capillaries and superficial veins connect directly with both ventricular cavities by discrete, deep drainage channels, the arterioluminal, the arteriosinusoidal, and the Thebesian vessels. Despite the presence of these deep channels and the existence of a favorable pressure gradient during systole, they are not used. Balance studies of coronary inflow and outflow have shown that approximately three fourths of the blood entering the left coronary artery drains into the coronary sinus. The remainder of left coronary artery inflow is recovered in the superficial (anterior cardiac) veins of the right myocardium that drain into the right atrium. Most of the right coronary artery inflow appears in these anterior cardiac veins and the remainder (10 to 20 per cent) drains into the coronary sinus. It is presumed that a similar pattern occurs in man.

Consideration of the mechanisms that control the oxygen supply to the myocardium involve certain difficulties not encountered in similar investigations in other organs of the body. The myocardial wall of the left ventricle not only furnishes the pressure head for driving blood into the coronary arteries but also may either offer phasic resistance to coronary flow or actually aid flow by its muscular contraction around the coronary vascular bed. Similarly, the right ventricle rapidly changes resistance to right coronary flow at the same time that left ventricular contraction presents blood to it under a pulsatile head of pressure. However, flow in either coronary artery will vary directly with the effective perfusion pressure head (aortic or central coronary pressure — right atrial pressure) and with the size or mean bore of the coronary bed. The bore of the coronary bed is regulated to increase flow by changes in the intrinsic smooth muscle of the coronary vessels as mediated by nervous, humoral, and metabolic influences (“active coronary dilatation”) and by a passive or mechanical mechanism arising from myocardial contraction during systole (“passive dilatation”).

Changes in the coronary circulation with acute or chronic alterations in stress make more economical use of the available oxygen and increase the available oxygen supply [coronary flow \times (artery — coronary sinus oxygen difference)]. First the biochemical and mechanical processes of the heart muscle adjust, so that a given myocardial oxygen usage results in greater external cardiac work. Second, the coronary vascular resistance decreases and coronary sinus extraction of oxygen increases. In this consideration, it is assumed that all coronary sinus blood has passed through a capillary bed. There are certain problems in the field of effective supply of oxygen, the solution of which has a practical application. Actually, considerable progress has been made in this direction.

The first problem is the identification of the direction and magnitude of the determinants of coronary flow that reside in the myocardial wall, i.e., the quantitative separation of the influence on coronary flow of the intravascular factors from mechanical effects of ventricular systole. This fractionation is of extreme importance, since under normal conditions the only other major factor affecting coronary flow is central coronary pressure, which ordinarily does not change greatly with exercise. Previous attempts to estimate separately the effects of vasomotor action and of myocardial contraction have been based on analysis of phasic flow curves in a coronary artery or vein. Such an indirect approach has led to the opposite conclusions that ventricular systole aids coronary flow and that it tends to throttle coronary flow. These deductions suffer from the assumption that the measured rate of flow in an epicardial artery and vein at the indicated time interval represents actual flow through the myocardium.

Recently, we have applied a technic in our laboratory that is thought to quantitate separately the effect on left coronary flow of the coronary vasomotor state and of ventricular contraction. In the open-chest dog the left coronary artery is perfused from a reservoir of blood at a constant pressure and the coronary flow quantitated by a rotameter, while flow in the coronary sinus is measured by a second rotameter as its blood passes to the right atrium through an indwelling polyvinyl cathe-
ter. Following coronary flow measurements in the beating heart, the flows are measured during prolonged diastolic relaxation induced by peripheral vagal stimulation to remove the mechanical effects of ventricular contraction. The results (of which, figure 2 is typical) have indicated that coronary flow increases invariably during asystole in both the left coronary artery (13-77 per cent) and in the coronary sinus (17-76 per cent). The same directional trends were observed in similar experiments with electric induction of ventricular fibrillation. These experiments have convinced us that ventricular contraction (myocardial action during systole) acts to impede coronary flow through the left ventricular wall; the extent of increased flow during asystole represents quantitatively the magnitude of the mechanical or passive factors limiting coronary flow; the new flow level represents that state of coronary dilatation related to the state of the intrinsic smooth muscle in the coronary vessels.

A second basic problem is the estimation of the amount of oxygen used by a ventricle when it is doing no external work. This measurement is vital to the determination of the economy of oxygen consumption by the ventricle, i.e., the mechanical efficiency of its operation, since as in any other muscle its efficiency is estimated by dividing its external work by the difference between its oxygen consumption during the beating state and during its relaxation. In the past, except for the oxygen usage of the relaxed or “resting” heart, these values have been available and many calculations made of cardiac efficiency in normal and pathologic states. Whether such values give even an indication of directional change for efficiency depends upon the magnitude of the unmeasured parameter. It occurred to us that the asystolic heart with its perfused coronary arteries might supply the physiologic situation in which the metabolism of the left ventricle during relaxation could be measured. Accordingly, the experimental preparation and procedures similar to those just described for indicating changes in coronary flow in asystole were used with the addition that the coronary arteriovenous oxygen difference was recorded con-

![Fig. 2. Reproduction of a record illustrating left coronary arterial inflow and coronary sinus drainage in asystole. The flows in the beating heart are 137 and 73 ml./min. for the left coronary artery and coronary sinus, respectively. With the induction of asystole by vagal stimulation (while perfusion pressure is held essentially constant), arterial inflow rises to 150 ml./min. and coronary sinus drainage to 111 ml./min. The time lines are one second apart.](http://circ.ahajournals.org/content/circulation/2/9/909/F2.large.jpg)
obtained for myocardial efficiency and their significance in a variety of clinical states until their fundamental adequacy can be ascertained.

A second interesting feature of these studies is that coronary sinus oxygen saturation does not begin to rise concomitantly with asystole but rather there is a lag of 10 to 15 seconds after which oxygen saturation rises to a new plateau in 25 to 30 seconds. This indicates that considerable oxygen is consumed by the left ventricle over and above the resting oxygen level from the onset of asystole to the apparent new equilibrium at 25 to 30 seconds. Presumably, this oxygen is used by the myocardium for performance of its work after the work period has been terminated, i.e., the left ventricle contracts an “oxygen debt.” This behavior of the coronary flow and oxygen usage of the myocardium during asystole is similar to that observed many years ago by Kramer6 for skeletal muscle as it went from a condition of rhythmic contraction to the resting state.

Consideration of the State of Performance of the Heart. Probably the most difficult and certainly the most controversial field in cardiology is the estimation of the state of performance of the heart.6 This consideration is particularly germane here, since depression of myocardial function or heart failure is undoubtedly most often the result of an inadequate coronary circulation even in the absence of mechanical obstruction to the coronary artery.

In seeking a method for determination of cardiac contractility or for evaluation of the dynamic state of the heart, the search for a correlative measurement of stroke work has led in various directions. Upon the basis of findings in the isolated heart, heart-lung preparation, and the open-chest dog in which cardiac size and cardiac work have been increased progressively by large and rapid blood infusions, the basic concept has been formulated that the energy of cardiac contraction (cardiac work) is a function of the extent to which myocardial fibers are stretched during the preceding diastole (diastolic volume). Since tension in a myocardial wall is related to the product of the pressure and radius in its ventricular cavity, curves of the relationship of ventricular end-diastolic pressure (or mean atrial pressure) to stroke work of the respective ventricle have been obtained also in these preparations. Recent expansion of the latter approach in the open-chest dog has indicated that each significant alteration of the circulatory state results in a new curve of relation of atrial pressure to stroke work. As evidenced by such left “ventricular function” curves the state of performance of the left ventricle is improved by mechanical increase in aortic resistance and by epinephrine injection, while severe anemia depresses ventricular function and unilateral depression of left ventricular function is related quantitatively to coronary insufficiency caused by constriction of the coronary artery. The validity of such curves is unquestioned as is their applicability to such preparations provided heart rate and the functional state of the myocardium are unchanged. This experimental approach serves as a useful laboratory method in differentiating between the normal and the depressed or failing ventricle. Without doubt, this relationship of either diastolic size or end-diastolic pressure to cardiac response is a fundamental property of the myocardium as it is in skeletal muscle. However, because of technical and other difficulties, neither of these measurements and comparisons has ever been made in the intact dog or man.

In the normal state, the stimulus to increased cardiac work is generally a combination of exercise and excitement which operates through neural and humoral mechanisms to change quickly and greatly the heart rate, size of great veins and atrial compartments, peripheral resistance, cardiac output, ventricular end-diastolic pressure, and cardiac size. While the crucial experiment admittedly has not yet been done, still there is no correlation in exercise between left ventricular end-diastolic pressure and stroke work; and left ventricular diameter (as determined by an intraventricular gage) and the ventricular diastolic volume (as estimated by x-ray) respond to the stress of exercise by becoming smaller rather than larger in diastole, irrespective of heart rate changes. These observations raise the question of the
relevance of the findings in the abnormal preparation to the problem of the regulation of the state of performance in the normal ambulatory animal or human being. Further advance in this field will depend upon adequate instrumental development for the determination of phasic changes in diastolic and systolic ventricular volumes in the normal state.

By the use of different approaches, certain data on basic flow have been established concerning utilization of the left coronary system of man and the dog. Left coronary inflow approximates 70 ml./100 Gm. of left ventricle per minute; coronary arteriovenous oxygen difference 10 to 12 ml./100 ml. of blood; left ventricular work 3.0 Kg.M./100 Gm. of left ventricle per minute. In the heart undergoing high stress, values approximating 12 Kg.M./100 Gm. of left ventricle per minute for maximum cardiac work are probably a reasonably accurate approximation. These figures were obtained in our laboratory during massive blood infusions in the normal dog and in the dog with a peripheral or aorta-caval fistula, and in man native to sea level or to a three mile altitude and exercising on a treadmill near exhaustion. Correct values for left coronary flow and myocardial oxygen consumption during natural maximal stress, such as exercise, are not available because of technical difficulties of instrumentation and application.

The extent to which increased oxygen extraction contributes to the available myocardial oxygen supply during increased stress is also undecided because of insufficient study. In some instances, such as an acute increase in systemic blood pressure through mechanical aortic constriction or a blood transfusion, the oxygen level of the coronary sinus is not significantly altered despite a considerable increase in systemic blood pressure, left coronary flow, left ventricular work, and oxygen usage. In the presence of acute pulmonic stenosis or aortic stenosis (central to the coronary ostia), in which the central coronary pressure is not elevated, the left coronary flow rises but oxygen content of the coronary sinus drops considerably, and most of the remaining oxygen is extracted. If the stenosis is severe enough there will continue to be an increased coronary flow and extraction of oxygen from the coronary circulation even if, prior to the induced stenosis, the control left coronary inflow is increased 2 to 3 times by raising the central coronary pressure to a very high level. In the heart failing acutely or chronically, oxygen saturation of the coronary sinus is invariably decreased. On the other hand, it is easy to increase considerably the oxygen content of the coronary sinus by injecting certain drugs such as epinephrine and norepinephrine intravenously or directly into the coronary artery. The increase in oxygen saturation of the coronary sinus is generally, although not necessarily, associated with an augmentation of the coronary inflow which supplies oxygen to the needy myocardium in excess of its metabolic demands.

It is exceedingly important to know the level of the oxygen content of the coronary sinus or coronary arteriovenous oxygen difference. Although extraction of this small volume of oxygen cannot increase greatly the myocardial oxygen supply, knowledge of its level enables an estimation of the balance between dilatation arising as the result of increased metabolic requirements in the heart and dilatation from the effects of substances on the smooth muscle of the coronary vessels and on the extent of extravascular compression. If the substance that causes dilatation and increased coronary flow operates mainly through the latter mechanisms, then it will be identified by the fact that as coronary flow increases, oxygen content of the coronary sinus blood decreases and the coronary arteriovenous oxygen difference decreases. This might be termed "benign dilatation" and is obviously an excellent situation for the heart, in that it obtains its blood flow cheaply. If, on the other hand, the increase in oxygen supplied to the myocardium by the coronary circuit during stress is less than the increased volume of oxygen used by the myocardial cells, the arteriovenous oxygen difference of the coronary increases. This operation is relatively expensive to the heart and might be called "malignant dilatation." This type of analysis is now being applied to various physiologic states and should
be helpful in the evaluation of the fundamental action of drugs.

Although we cannot as yet weigh the relative role played by these factors in promoting the oxygen supply to the heart in normal stress, such as exercise, there are certain general patterns of hemodynamic responses of the normal heart and of the pathologic nonfailing heart under increased and decreased stress that merit some consideration.\(^7\) In acute hypertension, coarctation of the aorta, increased venous return (whole blood infusion), acute and chronic anoxia, acute and chronic anemia, a chronic peripheral arteriovenous fistula, thyrotoxicosis, and intravenous injection of epinephrine or norepinephrine, there is an increase in the cardiac output, cardiac work, and cardiac oxygen usage. Concurrently, the inflow of the left coronary increases while its vascular resistance decreases. Fractionation of the coronary flow increase between active vasomotor change and passive change in the coronary bed has been attempted only in the situation of an acute elevation of aortic blood pressure and in the case of hypoxia. In the first instance, most of the coronary flow increase arises from an increase in central coronary pressure and active coronary dilatation; in the second case, reduction of myocardial compression and relaxation of smooth muscle in the coronary vessels appear to be equally potent in promoting coronary flow. An exception to this general picture of coronary compensation to increased stress is that of chronic hypertension, in which cardiac output, oxygen consumption, and left coronary flow are unaltered while coronary resistance to flow increases. This deviation is explainable if it is assumed that such hearts with known coronary artery disease have an increased amount of perfused nonmuscle tissue. A second exception is the failing rheumatic, arteriosclerotic, and hypertensive heart, or the acutely failing heart in the heart-lung preparation. These are characterized by a reduction in the output and work of the heart and a normal or mildly increased left coronary flow, while oxygen usage of the left atrium and left ventricle is normal in chronic failure and increased in acute failure. These hearts appear to have lost in part their ability to convert aerobic energy into cardiac work. This deviation is based presumably on the fact that in these hearts that are hypertrophied there are fewer capillaries per unit of myocardium to carry the oxygen and coronary flow.

Interest has been increasing in situations of decreased cardiac stress such as hemorrhagic hypotension and hypothermia.\(^8\)\(^9\) In these states, cardiac output, cardiac work, and cardiac oxygen usage decrease, as does the left coronary inflow. As compared with other vascular beds, the heart appears to be relatively protected, since the ratio of coronary flow to cardiac output is increased considerably. The intracardiac factors determining coronary flow here have not been quantitated separately. Although many oxygen values have been taken from the coronary sinus, the results are too erratic to warrant interpretation.

It has been indicated by some investigators that in sustained hemorrhagic hypotension and in hypothermia, despite the relative maintenance of coronary flow, myocardial depression and failure are present, as evidenced by a rising atrial pressure and cardiac dilatation.\(^10\) Since these parameters can be reversed by increased left coronary inflow without change in blood pressure or blood volume or by intracoronary injection of a sympathomimetic amine (Aramine), this failure is believed consequent upon an insufficient coronary flow. Although one does not question the responses noted, it must be borne in mind that the various surgical insults incident to such an experiment, in addition to the hemorrhage, can in themselves place the heart in failure. Actually, in neither of these situations have we ever observed a rising atrial pressure.

Blood transfusion for the restoration of a normal hemodynamic state often presents a desperate therapeutic problem. In hypotension produced by acute, severe blood loss, it is necessary to restore an adequate circulation to vital areas such as the brain and myocardium as rapidly as possible. The possibility exists that intra-arterial and intravenous transfusion could have quite different hemodynamic effects. The preferential use of the intra-arterial route in acute severe hemorrhagic shock has been
proposed on the assumption that intra-arterial transfusion would produce a more rapid increase in systemic pressure as a result of a hydraulic effect, so that perfusion of the coronary bed would be more quickly and effectively re-established, thus favoring the improvement of myocardial function. Some also feel that a larger volume of blood could be transfused by the intra-arterial route without producing dangerous elevations of venous blood pressure and right ventricular dilatation. However, the experimental studies on the effects of comparable blood infusions alternately by the arterial and venous routes in the same dog do not substantiate this view. In our laboratory and elsewhere, the intra-arterial route did not elevate left coronary flow or arterial pressure either more rapidly or more effectively than the intravenous route. Similarly, the route of infusion did not change the effect on either right or left atrial pressures or pulmonary arterial pressure, and excessive elevation of right ventricular end-diastolic pressure (cardiac dilatation) did not occur. These findings were observed in the dog with acute hemorrhagic hypotension, in the dog with prolonged hemorrhagic hypotension, and in the dog at the point of death. It must be borne in mind that the equal effectiveness of the two routes of transfusion does not indicate whether the coronary circulation is insufficient during severe oligemic shock.

Observations in ventricular fibrillation demonstrate an extreme and sustained myocardial resistance to death or to irreversible processes over a long period of time. During fibrillation without coronary perfusion at body temperature fibrillatory motion eventually ceases and cardiac adenosine triphosphate and glycogen levels become minimal; but if coronary perfusion is re-established one hour or more later, within a few minutes strong fibrillatory action returns, as does the resynthesis of high energy phosphate. The heart now uses about half the oxygen as the beating heart and a normal rhythm can be established by countershock. It is of particular interest that dogs will survive after hours of ventricular fibrillation in controlled deep hypothermia in which use of myocardial oxygen is greatly decreased and with only an intermittent and very low level of coronary perfusion. These observations suggest that prolonged ventricular fibrillation is not dangerous in itself in the presence of adequate myocardial oxygenation.

Physiologic Basis for Surgical and Other Procedures. After coronary artery occlusion, the ventricles are likely to go quickly into irreversible ventricular fibrillation or the hearts that survive this critical period may remain hypodynamic, with resulting limited work tolerance and large residual cardiac pain. It is presumed that the hearts of such individuals have too much infarcted tissue and too little collateral development. A most important problem is the evaluation of the effectiveness of surgical (and physiologic) procedures designed to stimulate collateral anastomoses in this situation.

Before assessing the physiologic implications of such surgical therapy for coronary occlusion, one must take cognizance of the natural large compensatory mechanisms that protect the heart before and after coronary artery occlusion. Apparently, the heart adopts the prophylactic measure of setting up or enlarging anastomoses between its own coronary arteries without the stimulus of coronary occlusion or insufficiency. In this connection, fundamental observations show that in the presence of anemia, cor pulmonale, cardiac hypertrophy, or valvular disease the incidence of intercoronary collateral anastomoses in injected human hearts is increased greatly over that in the normal human heart and, actually, in some instances, their frequency of appearance may approximate that with coronary artery occlusion or narrowing. A similar augmentation of the collateral bed of the coronary artery in pigs and dogs with induced anemia has been observed by injection and physiologic studies.

Our knowledge of compensatory changes in the coronary system following coronary occlusion is derived largely from the dog and pig. If blood is allowed to flow from a major branch (descendens or circumflex) of the left coronary artery distal to the point of its occlusion, this retrograde flow approximates within the first few minutes only 2 or 3 ml./min. of fully oxygenated blood that arises in
the other coronary artery. If the heart survives, the retrograde flow of oxygenated blood increases quite slowly to double within 48 hours and, within four weeks, to approximate the normal inflow into that coronary artery before its occlusion. In this situation, injection studies show that the intercoronary arterial collateral vessels increase greatly in size, number, and length, and most collateral flow comes from the right coronary artery or from the other major branch of the left coronary artery. Whether the increase in collateral flow is through pre-existing, nonfunctioning collateral vessels or through newly formed channels, or whether the latter ever develop, has never been determined.

This slow development of collateral circulation for as long as a month after occlusion may mean that a relatively small amount of collateral flow will maintain a viable myocardium, for many of these hearts survive with minimum infarction. This contrasts with the situation in the femoral and carotid arteries, in which collateral functioning reaches large values within one to two days after artery ligation.

Table 1 illustrates some of the attempts made to enhance the collateral circulation in the presence of coronary insufficiency.\(^{14}\) In this regard we are greatly indebted to Dr. Beck and associates for making available to us much unpublished data. Some of these procedures have been applied to selected patients after a coronary occlusion and who have had persistent angina pectoris and gross work disability. Improvement is reported in many instances. The criterion of success for any of the maneuvers should be a considerable reduction in the number and size of infarcts. These parameters are difficult to evaluate in human beings. In the dog, however, information on these points has accumulated from a number of laboratories including our own, and some of the trends are set forth in table 1. Ligation of a major ramus (circumflex or descendens) of the left coronary artery alone causes a 70 per cent mortality within the first hour, and chronically there is considerable infarction. If partial or complete occlusion of the coronary sinus or its arterIALIZATION immediately precedes acute ligation of the coronary artery, the immediate mortality is reduced considerably. Chronic ligation of the coronary sinus, arterIALIZATION of the coronary sinus, or myocardial implantation of an internal mammary artery followed by coronary artery ligation also leads to a significant reduction in mortality and in the number and size of

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Surgical situation</th>
<th>Ligated coronary artery ramus</th>
<th>No previous coronary artery ligation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mortality</td>
<td>Infarction</td>
<td>Anatomic collateral vessel</td>
</tr>
<tr>
<td>Acute</td>
<td>Coronary sinus open</td>
<td>70%</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Coronary sinus pressure increased</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Coronary sinus ligated</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aorta-sinus shunt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic</td>
<td>Coronary sinus open</td>
<td>70%</td>
<td>Gross</td>
</tr>
<tr>
<td></td>
<td>Coronary sinus ligated</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aorta-sinus shunt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic</td>
<td>Internal mammary artery imbedded in myocardium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic</td>
<td>Application of extracardiac tissue to myocardium—muscle, lung, intestine, pedicle skin flap</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic</td>
<td>Application of mechanical and chemical irritants to myocardium—abrasions, gauze, mica, phenol, tale, silver nitrate, asbestos</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic</td>
<td>Anemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic</td>
<td>Sham operation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TABLE 1.—Surgical and Physiologic Maneuvers in the Normal Heart and in the Heart Following Coronary Artery Ligation
infarcts. Application to the epicardium of various types of extracardiac tissue and of mechanical and chemical irritants in a chronic preparation also reduces mortality and infarction in the presence of subsequently induced occlusion of the coronary artery. Accordingly, it is deduced that these prior surgical maneuvers give sustained (and in the case of coronary venous maneuvers, immediate) protection against ligation of a major branch of the coronary artery.

If a heart can be benefited by such surgical procedures, then it should be helpful to have in mind the possible ways in which they could protect the heart. This consideration should be aided by reference to figure 1 in which are shown schematically the anatomic details of the coronary circulation. In the case of the coronary venous maneuvers, the protection could arise immediately from the creation of pressure relationships that promote passage of blood from the superficial coronary veins in retrograde fashion through the capillary bed and into the deep drainage system. Possibly, with these and other procedures, the benefit could arise from a small increase in blood flow through intercoronary and extracardiac collateral circulation established by the surgical procedures. Finally, the cardiac improvement could arise from the early protection that the procedures might give against ventricular fibrillation in the presence of coronary occlusion, and without change in collateral blood flow, thus allowing time for additional collateral circulation to develop and sustain the heart.

Let us now consider the available experimental data that may help to indicate which of these three physiologic possibilities is used to protect the heart against coronary occlusion in the presence of surgical maneuvers. There are no critical experiments to indicate that with the acute coronary venous maneuvers protection against fibrillation is supplied by blood flowing in a retrograde direction from coronary vein to coronary capillary to ventricular cavity. Acute perfusion of the coronary sinus with arterial blood at or near mean aortic pressure, or acute ligation of the coronary sinus, in each case being followed by acute ligation of the left coronary ramus, is characterized by venous congestion of the left heart with an increased coronary venous pressure equal or equivalent to the aortic pressure, a diffuse myocardial hemorrhage (with the exception of the septum which remains pink in color), and a sizable reduction in left coronary inflow. When the peripheral portion of the occluded coronary artery is permitted to bleed externally, the volume of back flow (15 to 26 ml./min.) of highly reduced blood is increased greatly over that following acute ligation of the coronary artery alone; this blood can be shown to have traversed the capillary bed of the occluded coronary artery in a reverse direction. There is no proof, however, that when the ligated coronary artery is not permitted to bleed externally, flow from the superficial coronary veins will be diverted through the capillary bed of the left myocardium. Actually, the development of extreme myocardial embarrassment, together with the fact that most of left coronary artery inflow and the blood entering the coronary sinus from the shunt can now be recovered in the anterior cardiac veins of the right ventricle, strongly suggests, but does not prove, that the deep ventricular drainage channels are not used.

Hearts in which either chronic ligation or arterIALIZATION of the coronary sinus has been combined with chronic ligation of the coronary artery have given no further evidence on the possibility of utilizing deep drainage channels of the heart or developing superficial collateral circulation. The coronary hemodynamic status is very similar to that following chronic ligation of the coronary artery alone; that is, the retrograde flow into the occluded coronary artery, which was initially highly venous, is now large in volume, arterial in type, and arises in the other coronary arteries.4

Studies5 on dogs prepared by the Beck technic with a long-term aorta-coronary sinus shunt have given some positive evidence on the mode of protection against subsequent acute ligation of the coronary artery. If, up to five weeks after the second stage of the operation, a major coronary branch is occluded acutely and then its peripheral end is permitted to bleed, flow from the graft through
the collateral bed is considerable and the blood is highly unsaturated. This collateral flow with the graft open is greater than with it clamped, thus indicating that the graft continues to function. However, when the fistula is clamped acutely, collateral blood flow from the acutely closed coronary artery is now arterial in type and exceeds in volume the 2 to 3 ml. draining from an acute ligation of the coronary artery alone. Dogs studied in this way after more than five weeks and up to 1 year after coronary sinus arterIALIZATION show still further increase in collateral flow; the blood is now arterial and clamping of the graft does not affect retrograde flow, indicating that the graft has lost functional contact with the coronary bed. Most of the blood can be shown to come from the other coronary arteries, and its volume is far in excess of that which obtains in the normal dog in which a coronary ramus has been acutely ligated. In addition, injection studies in such hearts show an increase in the anatomic vascular bed. These observations, recently confirmed, suggest that arterIALIZATION of the coronary sinus has stimulated intercoronary artery collateral development which functions for some time in the presence of nonligated coronary arteries. As indicated in table 1, there is also considerable evidence to suggest that a similar augmentation of anatomic and functional collateral vessels follows the chronic induction of the various maneuvers indicated, including chronic anemia and sham operations. However, one must emphasize that with none of these procedures is the injected anatomic collateral bed or the retrograde flow of the order of magnitude observed with chronic ligation of the coronary artery alone. With chronic ligation of the coronary artery, this back flow approximates 60 to 80 ml./min.; with the coronary venous maneuvers, 12 ml./min.; with the other procedures, 8 to 9 ml./min.; with acute ligation of the coronary artery alone, 3 ml./min.

From the preceding discussion, it would appear that a number of surgical procedures give a certain degree of immediate and sustained protection against subsequent ligation of a major coronary ramus. Chronic coronary venous maneuvers, local application of myocardial irritants and of extracardiac tissue, and induction of anemia cause considerable development of anatomic collateral vessels and, apparently, also of functionally significant coronary artery anastomoses, as shown by the considerable increase in retrograde flow when a coronary artery branch is now acutely ligated and permitted to bleed. However, one must emphasize with equal vigor the uncertain aspects of these experiments. Our analysis demonstrates only that collateral development occurs on the arterial side of the coronary circuit and presumably at the arteriolar level, but it does not necessarily show that the blood collected from retrograde bleeding of the centrally occluded coronary artery has traversed the capillary bed of that artery when the artery is not permitted to bleed. If it did traverse the capillary bed, it could at most supply about 7 per cent of the oxygen normally available to that region. If it is this volume of oxygen that gives protection against fibrillation and death, then the factor of safety supplied by the maneuvers is small, for in a heart with an acutely ligated coronary artery alone the estimated oxygen supply to the potentially infarcted zone is 3 per cent of normal, and most of these hearts die. The measurement of change in capillary blood flow following these maneuvers that might yield conclusive proof of the functioning of the collateral bed, to our knowledge, has never been made. In the case of such procedures as coronary sinus ligation and arterIALIZATION or application of epicardiac irritants, it does not seem to be possible to do this experimentally. However, the effectiveness of a skin pedicle flap, an artery implant, or an intestinal loop in promoting capillary flow through the potentially infarcted myocardium might be tested in the chronic situation by observing the change in coronary sinus flow before and after clamping of the extracardiac potential source of blood. Actually, in our laboratory in 2 dogs with chronic skin pedicle flaps applied to the left ventricle, subsequent clamping of the pedicles did not change the coronary sinus flow. This might seem to be a critical experiment, since there is no question about the establishment of vascular continuity between extracardiac tissue and the myo-
cardium; nevertheless, the beneficial effect of the graft may still be attributable to its acting as a bridge between the branches of one coronary artery and those of another, so that clamping of the extracardiac tissue would not alter flow of the coronary sinus. The fact that an equivalent intracardiac collateral development appears to follow a sham operation, also raises the question of the specificity of any of these maneuvers. Since in most instances death follows coronary artery ligation within 24 hours, we must still entertain seriously the third physiologic possibility mentioned earlier: that the benefits of reduced mortality and infarction arise in part from the protection that the procedures themselves might give against ventricular fibrillation in the presence of coronary occlusion (that is, without an immediate increase in retrograde flow), thus giving additional time for collateral circulation to develop and sustain the heart.

Since these surgical procedures afford protection to the dog heart against subsequent coronary artery ligation, it is possible that they might protect the human heart if used prophylactically. However, it does not necessarily follow that they will be of positive benefit to human beings with occlusive coronary artery disease. This view arises from a number of considerations, chief of which is that in these experimental studies coronary artery ligation was always preceded by the surgical maneuver, whereas in the human being, there is time after acute coronary artery occlusion for natural maximal collateral development before the surgeon attempts to arterialize the coronary sinus.

REFERENCES


Current Research and Problems of the Coronary Circulation
DONALD E. GREGG and DAVID C. SABISTON, JR.

Circulation. 1956;13:916-927
doi: 10.1161/01.CIR.13.6.916
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1956 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/13/6/916.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/