Anatomical and Physiological Considerations in the Development of a Collateral Circulation to the Myocardium

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1. Introduction

I wish to present our concept of collateral circulation in the heart as it is related to the problem of coronary artery disease in man. The physiological information has been largely derived from studies on the dog heart. We believe that the information derived from these physiological studies is directly transferable in building up a concept of the clinical problem in man, including the evaluation of methods of therapy. I wish to acknowledge that Dr. Claude S. Beck has been the originator of the surgical approach to the treatment of coronary disease and has been the chief proponent of the studies that have been carried out during the past 24 years.1

The development and application of precise physical methods of accurately recording and measuring fluctuating intravascular pressures by Frank, Wiggers and Hamilton has provided much basic information about normal cardiac function and hemodynamics. The further application of these principles and refinement of methods for the study of the coronary circulation by Gregg, Green and coworkers has provided accurate information about the coronary circulation in the normal heart.2 The further application of these and similar methods of study must ultimately provide us with the complete knowledge of the changes that take place in the myocardial circulation when coronary arteries are progressively obstructed. Furthermore, the physiological information will then clearly explain anatomical findings and be integrated into a clear understanding of the total aspects of coronary disease. I wish to acknowledge that Drs. R. W. Eckstein and D. S. Lehnninger have made especially significant physiological contributions in various phases of this problem.

2. Historical

It is self evident that no rational concept of collateral circulation could exist prior to the understanding of the circulation of blood as first reported in detail by William Harvey.3

Our basic knowledge about collateral circulation of the myocardium, which may be considered the emergency blood supply available when the normal blood supply is interrupted, involves anatomical, physiological and metabolic areas of study. As various isolated fragments of information became known about the anatomy of the vascular system of the heart and about the function of the myocardium, various hypotheses were formulated...
to indicate possible alternate channels of blood flow when the normal flow is interrupted. These hypotheses have led to a considerable conflict of ideas which are being resolved with the advent of reliable methods of measuring blood flow.

The earliest hypotheses of the mechanism of collateral circulation were the result of purely anatomical studies. The existence of anastomoses between coronary arteries was known in the 17th century during which period the exploration of the finer ramifications of the vascular system by the injection of dyes was begun.

In 1706 and 1708 the publications of Vieussens and Thebesius described the channels connecting the coronary vessel directly with the chambers of the heart. The anatomical knowledge of these vessels later led to a long and fruitless controversy as to their functional significance, especially their possible role as avenues of collateral circulation. However, in the year 1880 Ludwig Langer, in a report of his studies of the Thebesian channels in injected specimens of human hearts, made the following observation concerning the anastomoses of coronary arteries:

"I was able to demonstrate in several hearts injected with a fine resin mass several visible connecting branches between the right and left coronary arteries. These connecting branches ran transversely across the front surface of the heart and lay immediately under the epicardium. In these vessels the various colored masses which were injected into the coronary arteries met before a filling of the capillaries or veins took place." Langer continues: "The mentioned communications of coronary arteries with each other is not so unusual when one considers that the blood vessel system of the heart is not represented as an isolated whole. The vasa propria of the heart, as is known, anastomose much more with the vessels of the neighboring organs in a rich manner and indeed not only in the venous domain but also in the arterial territory. Such an anastomosis exists with the vessels of the pericardium as well as with the bronchial vessels and with the vessels of the diaphragm through the medium of the vasa vasorum of the large vessels emerging from the heart. By injection of the coronary arteries there is regular filling of the vasa vasorum of the cavae, the aorta, the pulmonary arteries and veins." Langer concludes: "The described anastomoses of the vasa propria of the heart with other vessels is noteworthy in clinical relationships. They provide the possibility that the heart can also be nourished with blood through collateral circulation when one or both branches of the coronary arteries are made impervious as a result of an atheromatous process—and it is well known that the atheromatous process is unusually frequent in the coronary arteries."

F. H. Pratt, working in W. T. Porter's physiology laboratory published some interesting observations and ideas in 1898. "Many anatomists and physicians still contend in the face of conclusive experiments that the coronary arteries are not truly terminal. How else can such immunity from infarction be explained? What but a collateral circulation through branches freely communicating with other coronary arteries could have kept the ever active muscle from decay? The failure of the distal end of
a severed coronary artery to bleed in the profuse way that indicates a free communication with other vascular areas; the fact that infarcts frequently though not invariably follow the embolism or thrombosis of these vessels during life; and most conclusive of all the easy production of infarcts by ligation of coronary arteries, have not convinced some minds. They cling to the occasional freedom from infarction after thrombosis or embolism and not seldom attempt to strengthen their position by pointing to the fact that one coronary artery can be injected from another. These writers forget what a terminal artery really is. They forget that terminal arteries, like all other blood vessels, communicate with their neighbors by capillaries."

"An artery is terminal, not because it has no communications with neighboring arteries but because this communication is of a particular kind. *Terminal* simply implies that the resistance in the anastomosing branches is greater than the blood pressure in the arteries leading to these branches. It is this resistance which makes an artery terminal. This concept is physiological and only secondarily anatomical. Only injections that *pass with great ease* can be considered as presumptive evidence against the terminal nature of an artery; and as a fact aside from rare abnormal cases injections pass from one coronary artery to another with difficulty or not at all. The advocates of *free anastomosis* of coronary arteries have indeed a difficult position. They must explain how infarcts can follow closure of freely anastomosing vessels. We who believe in the terminal nature of these arteries need only to explain why the closure occasionally fails to produce infarction. An explanation of this can now be given." Pratt was referring to his demonstration that the cat myocardium will resume regular contractions and continue beating for a long time if either the right ventricular cavity or the coronary veins of the non-working cat heart are perfused with defibrinated oxygenated blood under low pressure. Under these circumstances it was presumed that the myocardium was nourished by retrograde flow through the capillaries via the Thebesian and coronary veins. Pratt stated further "It is also possible that a very gradual closure of an artery might permit the gradual dilatation of the communicating vessels until the resistance in them is low enough to divert a part of the blood in the neighboring areas into the anemic district; and thus gradually establish sufficient collateral circulation to keep the part alive. These possibilities have long been recognized."

In 1907 Hirsch and Spalteholz\(^9\) experimentally ligated the descending ramus of the left coronary artery of dogs and monkeys, and on the basis of injection studies and the size of the resulting infarcts concluded that there was a functional collateral circulation from other coronary arteries. They were of the opinion that the anastomoses of the dog were comparable to those found in the human heart.

An observation of significance consisting of a single case report was recorded in the literature in 1903 when Ch. Thorell\(^10\) described the heart of a man of 68 who died of carcinoma. At autopsy both coronary arteries were found to be obliterated in their proximal portions. The existence
of extensive pericardial adhesions was thought by him to have provided vascular channels for an adequate collateral circulation from the vessels of the pericardium.

Wearn,\textsuperscript{11} studying the anatomy of the Thebesian vessels in human hearts, revived the Thebesian back flow hypothesis of Pratt and concluded that “in the event of gradual closure of the orifices of the coronary arteries the Thebesian vessels can supply the heart muscle with sufficient blood to enable it to maintain an efficient circulation.”

In 1930 Leary and Wearn\textsuperscript{12} reported two cases of complete chronic occlusion of both coronary arteries at their orifices and concluded: “The only adequate explanation of the ability of these patients to live and work rests upon a belief that the Thebesian veins have supplied the compensatory circulation necessary for the functioning of the heart muscle.”

In 1932 Moritz, Hudson and Orgain\textsuperscript{13} reported the findings in four human hearts with partial or complete obliteration of the pericardial sac by fibrous adhesions in which the coronary arteries had been injected with a colloidal suspension of lampblack and anastomoses were found to exist traversing the adhesions between the heart and pericardium. This was an anatomical demonstration of the acquired extracardiac vascular anastomoses suggested by Thorel.

3. Early Studies in the Surgical Laboratory

Experimental studies were begun by Claude S. Beck in February of 1932 in an attempt to produce adhesions between the heart and other tissues for the purpose of providing a collateral vascular bed as a source of collateral circulation to the myocardium. The work was suggested by the demonstration of Moritz, Hudson and Orgain of anastomotic vascular channels in adhesions between the heart and pericardium. Tichy and Moritz joined as collaborators in these first experimental studies the results of which were published in 1935.\textsuperscript{1, 14

In this work it was clearly demonstrated that vascular connections could be produced between coronary and extracoronary vessels. The more exact nature of the vascular connections were not determined in these earliest studies. The procedure appeared at this time to protect the heart but no precise method of measuring the degree of protection had been worked out. However, as a result of this work an idea was born demonstrating the feasibility of a surgical procedure for the purpose of improving the blood supply to the myocardium. Thus was opened a new field for study in the domain of biology and medicine.

Harold F. Robertson\textsuperscript{15} in 1934 published the results of some studies in which he attempted to ligate the main venous channels of the heart in one to three stages and later attempted to ligate all the coronary arteries in several additional stages. He observed that “when animals were reopened and adhesions separated there was much hemorrhage, the underlying heart became cyanotic and appeared to be nourished by the adhesions.” He concluded that these experiments showed that the “myocardial nutrition distinctly depends upon the vessels contained in the adhesions.” This conclu-
sion was a matter of opinion since there were no controlled statistical data to support the opinion and no anatomical studies of the condition of the vascular system as altered by the procedure. Regarding any possible beneficial effect of venous ligation he later concluded that the “myocardial changes produced would not prove beneficial to a heart already suffering from other pathology.”

All of the earlier experiments pointed to the need of a better understanding of collateral circulation in the heart. However, at this date there was still the maximal diversity of opinion about collateral circulation in the normal heart and in fact there were no anatomical or physiological studies to indicate that a collateral circulation does develop in response to arterial occlusion. New methods of study were needed to test the various and conflicting ideas about collateral circulation to the myocardium. The laboratory studies were continued and in 1936 additional anatomical information was published.

In these studies chronically occluded coronary arteries of the dog heart were injected with barium sulfate gelatin mixtures according to the method of Louis Gross. This method did not visualize capillaries and veins as did the water solution of iron ferrocyanide (Prussian Blue) used in the previous experiments. The barium sulfate gelatin mixtures passed through arterioles with difficulty or not at all if they measured less than 70 micra in diameter in the histologic sections of the injected heart.

As a result of these studies two phenomena were clearly demonstrated, it is believed for the first time in the mammalian heart: (1) The identification of newly formed arteriolar connections between coronary artery system and the internal mammary system. These were found in preparations in which the subternal muscles with the associated mammary arteries had been detached from the sternum, sutured to the surface of the abraded heart and the coronary vessels constricted. The anastomoses were large enough to permit free passage of the barium gelatin mixture. The ability to obtain such anastomoses was limited to a small percentage of the preparations, presumably due to the difficulty of obtaining the optimum conditions for the development of such a collateral circulation. When obtained the collateral injection flow passed with sufficient ease to fulfill Pratt's postulate that the anastomosing vessels probably serve as a pathway for functional collateral circulation.

(2) The demonstration of tremendous enlargement of anastomotic channels between chronically occluded coronary arterial segments and unoccluded coronary arteries. These vessels could be identified by their increased diameter and tortuosity, indicating increase in length as well as in diameter. Histologically they bore no resemblance to the arteriole normally found in the same situation, being lacking in smooth muscle and elastic tissue. By dissection they could be shown to connect coronary arteries. These vessels were shown to measure as much as 14 times the maximum diameter of normal intercoronary anastomoses.

The results of these studies were again of an anatomical nature and did
not answer the question as to the specific role of a surgical procedure in augmenting collateral coronary circulation. The hypothesis that intercoronary communications might provide collateral circulation seemed to be proved by the great enlargement of these anastomoses. Furthermore, the mathematics of fluid flow in tubes would indicate that the per second volume flow through a collateral vessel varies as the (diameter)^4, other factors being constant. This gives a considerably greater significance to the observed enlargement of the anastomotic channels. The observations reported in this study “suggest the possibility that there may be a chemical or metabolic factor elaborated in the ischemic area which exerts an influence on adjacent arterial anastomoses.”17

In 1940 Burchell18 confirmed the enlargement of collateral channels bridging around chronic arterial obstruction placed below the primary branches of the main coronary arterial divisions in dogs. Basal anastomoses were demonstrated without difficulty but in his experiments any flow through tissue adherent to the epicardium was thought to be minimal or non-existent. He pointed out that the theory of reestablishment of cardiac function after healing of an infarct had not been stressed since the work of Hirsch and Spalteholz in 1907.

4. Confirmatory Studies in the Human Heart

In 1938 Monroe J. Schlesinger19 published information gained from injection studies of human hearts showing that as in the dog heart anastomoses enlarge as a result of stenosis or occlusion of major coronary arteries. Age alone was not established as a factor causing enlargement as had earlier been suggested by Gross. By a continuation of the same method of study and analysis a significant new finding was described in 1951 by Zoll, Wessler and Schlesinger20, namely, that in the absence of arterial disease in the heart that significant enlargement of intercoronary anastomoses occurs in chronic anemia, chronic pulmonary disease with cor pulmonale, cardiac hypertrophy, and valvular heart disease. It was concluded that cardiac hypoxia was common to all these conditions and this was regarded as the probable stimulus causing the enlargement of the intercoronary anastomoses.

This work led Blumgart et al21 to restudy experimentally the development of collateral circulation in the dog and later in the pig. They were of the opinion that the arterial anastomoses in the normal pig heart were more nearly comparable with those in the normal human heart as to size and distribution. The anastomoses of the normal dog heart were shown to be slightly larger. They reached the same conclusion as had been previously reported17 that chronic severe arterial narrowing leads to enlargement of intercoronary anastomoses, most readily demonstrable 12 days or more after the arterial obstruction although in some specimens noted at an earlier time.

Gregg et al22 had previously shown that significant increase in collateral flow frequently begins in the first 48 hours after an acute arterial occlusion.
5. Physiological Studies of Collateral Coronary Circulation

Let us return to the viewpoint of the physiologist. Tennant and Wiggers\textsuperscript{22} in 1935 noted that after ligation of a main coronary artery in the normal dog heart that the blood supply is so far reduced that contraction in the ischemic area invariably fails within one minute and Wiggers and Green\textsuperscript{28} state that this phenomena cannot be prevented by drugs that elevate aortic pressure or act upon collateral vessels.

Gregg, Green and Wiggers\textsuperscript{24} studied the pressure in coronary arteries distal to a ligature and found a pressure to be maintained at roughly one fifth of aortic pressure. From an analysis of the peripheral coronary pressure curves they concluded that the principal systolic rise was due to squeezing of the isolated arterial system by the ventricular contraction beginning in the isometric phase, rather than the result of transmission of blood and pressure through collaterals from sources approximating aortic pressure. They noted however that a "very small amount" of arterial blood bleeds back from the periphery of a divided coronary artery.

Stella\textsuperscript{29} in 1932 was unable to record any flow from the peripheral end of a divided coronary artery when all the other coronary arteries were briefly centrally occluded, indicating rather decisively that what backflow is present comes from other arteries. Wiggers\textsuperscript{26} reviewed his data on the question of collateral blood supply available to the myocardium and concluded: "When critically reviewed most of the experimental evidence favors the view that from a practical aspect the coronary branches are essentially terminal; anastomoses such as exist in normal hearts apparently have no functional value." However, Wiggers also said, "The existence of negligible collateral supply in normal hearts does not preclude the enlargement of minute potential communications nor the development of new ones when a main branch (of a coronary artery) is slowly occluded." Before writing this opinion Wiggers had seen a heart\textsuperscript{27} from the Beck laboratory in which an area of the myocardium to which the supply artery had been chronically interrupted was seen to be again vigorously contracting. Wiggers then offered the suggestion that the stimulus that might cause this hypothetical enlargement of collateral channels to be a "differential of pressure" between occluded arterial segments and sources of collateral blood supply.

6. Physiological Demonstration of Increased Intercoronary Collateral Circulation

Following the anatomical demonstration of enlargement of intercoronary anastomoses in 1936,\textsuperscript{17} some preparations were made in the Beck laboratory in which coronary arteries in the dog were chronically occluded and myographic studies were made of the surface of the heart over an area originally supplied by the occluded artery as well as peripheral coronary pressure records and backflow measurements from the chronically occluded arteries.\textsuperscript{28} Great increase in the peripheral coronary artery pressure at times approximating aortic pressure, and backflow measurements in amounts as much as 25 times expected in the normal were observed after chronic coronary arterial obstruction. This conclusively demonstrated by an objec-
tive method and for the first time "that following chronic occlusion of a major coronary arterial ramus that there develops a massive new collateral circulation capable of again supporting myocardial contractions."

Attempts were made to trace the source of this collateral. This proved to be difficult, but gave the following information: Two-thirds to nine-tenths of the blood coming into a chronically occluded arterial segment could be definitely shown to come from the unoccluded coronary arteries. It was not possible to accurately determine the source of one-tenth to one-third of the collateral except that the quality of the blood was indistinguishable from arterial blood on the basis of oxygen and carbon dioxide content. Some of it no doubt came from the septal artery and the remainder from extracardiac sources. These findings are in complete agreement with the anatomical studies showing great increase in intercoronary collaterals and only slight increase in extracardiac anastomoses.

7. The Surgical Problem of Augmenting Collateral Coronary Circulation

A. Abrasion of heart and pericardium

Getting back to the surgical problem, the most urgent task seemed to be to work out a method of accurately measuring the benefit of a surgical procedure designed to improve collateral coronary circulation.

A carefully controlled statistical study of mortality and infarction following a standard descending ramus coronary artery ligation was carried out. The results, in normal dogs were compared with the same ligation in animals that had previously been prepared by mechanical abrasion of the surface of the heart with a specially designed mechanical burr with removal of considerable amounts of epicardium.

The results of this study showed a 70 per cent mortality in the normal animals and a 38 per cent mortality in the prepared animals when the descending branch of the left coronary artery was ligated at its origin one to three weeks after the abrasion. Key et al. later had a comparable mortality of 78.3 per cent in an adequate series of descending ramus ligations in normal animals and found that previous removal of the epicardium and the application of a pedicle graft of jejunum from which the mucosa was removed reduced the mortality from the same ligation to 6.9 per cent. Even though the mortality following surgical ligation of a coronary artery depends upon many biological variables and therefore may not be the same in every laboratory or in the same laboratory, under altered circumstances, it is believed that the lowered mortality observed in the above mentioned studies, represent a significant difference in the behavior of the two groups of animals. This indicates clearly that previous abrasion protects the heart against acute coronary obstruction. In the latter experiments of Key et al proof must still be supplied that the pedicle graft is supplying a significant amount of blood to the ischemic myocardium.

B. Coronary sinus ligation

A variation of the retroperfusion of the coronary sinus was suggested by Gross and Blum i.e. ligation of the coronary sinus. Their studies sug-
suggested that coronary sinus ligation prior to left descending ramus coronary artery ligation reduced the amount of resulting infarction. Post mortem injection studies of the unoccluded arteries with barium sulfate gelatin mixtures showed better filling of the occluded arterial segment under the following circumstances: 1. After coronary sinus ligation alone or 2. After coronary sinus ligation followed by later descending ramus coronary artery ligation. These studies indicated that enlargement of intercoronary anastomoses occurred following coronary sinus ligation. It was their impression that coronary sinus ligation prior to coronary artery ligation reduces the amount of infarction, but the published data does not supply adequate proof of this impression.

In 1938 Gregg and Dewald showed in acute experiments that ligation of the coronary sinus greatly increases the pressure within the veins of the left ventricle to values approaching mean aortic pressure. Also that this procedure limits left coronary artery inflow mildly to considerably, and causes a marked increase in the retrograde flow from the periphery of a divided coronary artery. The retrograde blood was found to be very dark and to contain only approximately three volumes per cent of oxygen. They observed that coronary sinus ligation did not prevent the abrogation of myocardial contractions following coronary artery occlusion.

In July of 1941 Beck and Mako published the results of a study, that was adequately controlled, in which it was determined that if the coronary sinus is ligated several days to four months before descending ramus coronary artery ligation the mortality from the latter procedure is reduced from 70 per cent in the controls to 50 per cent and the size of the infarcts was reduced in the survivors that had previously had coronary sinus ligation. However, it was concluded that further studies should be done before considering this as a therapeutic measure in clinical coronary disease.

C. Acute arterial retroperfusion of the coronary sinus

In 1943 Roberts, Brown and Roberts studied the effect of acute retroperfusion of the coronary sinus of the dog's heart with arterial blood at aortic pressure. The principle was the same as had been shown by Pratt to restore a coordinated beat in the isolated non-working cat heart. They reported that the dog heart will continue to beat regularly and forcefully after extensive obstruction of coronary arterial inflow. No statistical comparison was made of the behavior of the heart with the arterialized coronary sinus as compared with the normal heart to prove their contention, but it was their reported impression that there was a striking protection against the immediate and early effects of acute coronary artery obstruction.

D. Chronic arterIALIZATION OF THE CORONARY SINUS

If the perfusion of the coronary sinus with arterial blood supplies a collateral circulation that protects the heart in acute laboratory experiments, Beck's contention would seem quite logical that chronic arterIALIZATION by anastomosis of a systemic artery to the coronary sinus might be of value in providing a more abundant collateral circulation than either coronary sinus ligation or abrasion of the epicardium. Such a procedure was de-
veloped in the Beck laboratory and tested by the coronary artery ligation mortality and infarction test.\textsuperscript{57}

A technique was developed to arterIALIZe the sinus by using a vein graft to bring arterial blood from the aorta to the coronary sinus. At a second stage the coronary sinus was narrowed to 2 or 3 mm. in diameter between the entrance of the shunt and the ostium in the right auricle. The technique was perfected to a degree that this could be done without the development of thrombosis, a complication which was a considerable problem in the earlier attempts. In testing the benefit of this procedure by descending ramus ligation a 70 per cent mortality was obtained in the control animals and only a 20 per cent mortality in the animals in which the vein graft was patent and feeding arterial blood retrograde into the coronary venous system which normally drains into the coronary sinus. As this test of benefit was extended to a larger series the mortality following descendens ligation was found to be 8.9 per cent in a series of forty-five animals.\textsuperscript{58}

\textbf{E. The Mechanism of Protection of Arterial Retroperfusion of the Coronary Sinus}

That this protection was due to increased collateral circulation was indicated by the actual measurement of increased collateral circulation by the backflow method previously described.\textsuperscript{28} After arterIALIZation of the coronary sinus there was found an immediate increase in the backflow from the divided coronary artery.\textsuperscript{29} The backflow during the first five to 12 weeks after production of the shunt was found to be blood only partly saturated with oxygen, indicating that it has passed through a capillary bed prior to entering the artery. During the above mentioned time interval clamping the shunt reduces the backflow. Beyond the five to twelve week interval the backflow was found to remain increased, to be again arterial in character and to be unaffected by clamping the shunt in either the amount of backflow or in the degree of arterIALIZation of the blood. Inter-coronary anastomoses were found to have increased in size while gradual sclerosis had taken place in the small veins of the outflow tract of the arterIALIZED coronary sinus. The venous sclerosing process gradually reduced retrograde flow through the myocardial capillaries until eventually all physiological contact is lost between the arterIALIZED sinus and the myocardia capillaries.\textsuperscript{40}

Early after arterIALIZation the retrograde flow offers protection against ventricular fibrillation when a coronary artery is ligated. This might be due to other factors than improved capillary blood flow in the ischemic myocardium but the marked reduction in the degree of infarction can only be interpreted as the result of improved collateral circulation.\textsuperscript{38, 41-45} The protection is much more striking than after simple coronary sinus ligation and has been observed to be present for one year.

Eckstein et al,\textsuperscript{46} by acute arterial perfusion studies, supplied the proof that was lacking in the Roberts' report regarding the beneficial effect of acute arterIALIZation of the coronary sinus in acute coronary artery occlusion. In control animals a 70 per cent mortality in one hour was found after
ligation of the circumflex artery, all the fatalities were due to ventricular fibrillation occurring within 10 minutes after the occlusion. In a second group with the coronary sinus arterialized at 50 mm Hg. pressure all survived for one hour. Eckstein and Leinhninger and co-workers discovered that the increased collateral provided in both the acute and chronically arterialized coronary sinus often prevented the maximal S-T deviation in the electrocardiogram after acute coronary arterial occlusion. In the animals with functioning shunts 75 per cent showed evidence of protection as compared with 25 per cent of a group of normal dogs. This per cent increased incidence of evidence of protection was present early after the sinus arterialization and also after late blood flow had ceased from the arterialized venous system to myocardium. The late protection was correlated with the increased intercoronary collateral flow.

Further light was cast on the modus operandi of the arterialization of the coronary sinus by evaluating the effect of a sham operation in which the complete arteriovenous shunt operation was done, but the shunt was ligated at the completion of the procedure. There was a definite increase of the retrograde circumflex flow averaging 6.9 cc./min. four to five weeks after the initial procedure as compared with 3.8 cc./min. in normal dogs. In these experiments no constriction of the coronary sinus was produced between the shunt and the ostium of the coronary sinus.

In the animals with A-V shunts and the coronary sinus opening narrowed to an external diameter of 2-3 mm., backflows of 11.0 cc. per minute were found after a comparable time interval. The increased backflow in the sham operations represents the dilating effect of the trauma of operation, comparable to the abrasion experiments, on the intercoronary anastomoses. Lesser degrees of trauma, as pericardiectomy and resuscitation from ventricular fibrillation do not always cause dilation of the intercoronary anastomoses.

Unfortunately the technical aspects of the chronic arterialization of the coronary sinus and the fact that the residual arteriovenous shunt introduces an added strain on the heart, impose limitations on the clinical application of this procedure and suggest the desirability of going back to a simpler procedure for clinical use.

F. Implantation of internal mammary artery into myocardium

Vineberg has confirmed the production of new extracardiac anastomoses by reporting the production of vascular communications between the internal mammary artery and the coronary vessels in over 50 per cent of preparations by placing the internal mammary artery in a myocardial tunnel and allowing it to bleed from the origin of the sixth intercostal artery into the tunnel. Vineberg is of the opinion that the blood flowing from the internal mammary does not lead to the formation of a hematoma within the myocardium, but that it finds its way almost immediately into the myocardial sinusoids and establishes a new circulation. Permanent vascular connections were shown to develop between mammary implant and both the coronary arterial and venous systems in a high percentage of prepara-
tions. Physiological studies showed that blood could be perfused, under constant pressure equal to the mean aortic pressure, into the coronary vascular system through an implanted internal mammary artery at the rate of 45 cc. per minute. Retrograde flow from the periphery of the implanted internal mammary artery in the living animal was found to be of the order of one cc. per minute. One of the most interesting findings was the development of intimal thickening in practically all the implanted arteries, the degree of which appeared to be inversely proportional to the flow in the vessel, and caused almost complete obliteration of the lumen in the end of the vessel where there was no flow.

On the basis of backflow, vascular injections and erosion preparations it appears that these anastomoses are about the same size as the largest intercoronary anastomoses occurring in the normal heart. On the basis of existing knowledge it would appear that the contribution of blood through these implanted internal mammary arteries is small compared with the collateral from other coronaries. However, such a contribution from extra-cardiac sources could become more significant as the total coronary arterial inflow becomes progressively reduced. It is doubtful that this would be the case with only one major coronary arterial ramus obstructed. Evidence is presented in the constant pressure perfusion experiments that some of the perfused blood passes through myocardial capillaries. There have been no measurements to indicate whether or how much blood may be shunted through arteriovenous communications that have been shown to develop under these circumstances. The crux of the matter lies in measuring the amount of blood that mammary artery implants contribute to chronically occluded arteries, as compared with the collateral from other coronary arteries. Such studies were carried out by Leighninger43 who found no increase over the normal backflow in these preparations and no measurable component contributed to the backflow from the implanted internal mammary artery. The implanted artery was patent in fifteen of twenty dogs studied. It is conceivable that the operation of implanting the internal mammary artery under different circumstances could stimulate the development of intercoronary collaterals.

G. Abrasion of Heart and Pericardium, Chemical Irritation and Partial Coronary Sinus Obstruction

Studies were again undertaken to evaluate the stimulation of collateral circulation by the simpler procedures of mechanical abrasion of the heart and pericardium, the use of chemical irritants, and partial coronary sinus obstruction.38, 43, 44 By this time it had become apparent from the studies in the normal control animals that the findings were contrary to the hypothesis of Pratt3 and others and also of Wiggers48 who said, "From a practical aspect the coronary branches are essentially terminal; anastomoses such as exist apparently have no functional value." For in sixty-five normal dogs studied the circumflex backflow varied greatly and measured from 0.4 to 21.0 cc. per minute; the median was 2.8 cc./minute and the average 3.8 cc./minute. The mean peripheral coronary pressure varied from 1/14 to 3/10 of the mean aortic pressure.40 When the electrocardiogram was
studied it was noted that in 20 per cent of normal dogs in the area of the greatest backflow that the maximal change in the S-T segment did not develop following simple circumflex occlusion, but that the maximum change did take place when the distal artery was opened and allowed to bleed back.

The failure of complete infarction of the supplied myocardium can now be explained as due to intercoronary collateral and nothing else. To date there have been no physiological observations to indicate that any collateral circulation occurs via the minute corrections between the terminal branches of the coronary arteries and the cardiac chambers in the normal heart or after chronic arterial obstruction. Pressure relationships would be favorable for such a flow from the left ventricle to the coronary artery during systole only when the coronary artery pressure is reduced significantly below aortic pressure. Any flow from the right ventricle into coronary arteries could occur only under the abnormal circumstances in which right ventricular pressure considerably exceeds intracoronary and intramyocardial pressure during systole.\textsuperscript{26, 49} Furthermore, no anatomical studies have to date revealed any enlargement of possible collateral channels from intracardiac sources in the presence of chronic arterial obstruction. It would seem that great enlargement of these channels would be necessary before a to and fro flow of this nature could possibly reach the myocardial capillaries, since the resistance to flow through the normal sized channels into occluded coronary arteries appears to be great.

In 41 dogs subjected to mechanical abrasion of the heart and parietal pericardium, the application of 0.2 gram of powdered asbestos and narrowing of the coronary sinus to a diameter of 2 to 3 mm., the average circumflex backflow was found to be 8.5 cc. per minute varying from 0.4 to 26 cc. per minute. Furthermore, 68 per cent of the dogs showed electrocardiographic evidence of protection.\textsuperscript{43, 44} What makes these experiments more significant and crucial is the fact that increased collateral was produced in the absence of arterial obstruction. Descending ramus ligation after preparation by this procedure resulted in a 26.6 per cent mortality in a group of 30 dogs as compared to 70 per cent in the control group of normal animals. In other words, the increased circumflex backflow provided by the procedure, while amounting to only 4.7 cc. per minute indicating approximately double the normal intercoronary collateral, represents the lifesaving factor in 43 per cent of the animals so prepared. And what is equally important this small increment in collateral saves much myocardium that would otherwise be converted into the scar tissue of infarction. The increase in basic collateral saved life and myocardium. After the acute occlusive episode there is the opportunity for the continued gradual enlargement of anastomotic channels so that maximal function can again be restored in the ischemic myocardium. Gregg and Sabiston\textsuperscript{46} have estimated that in a heart with an acutely ligated coronary artery the oxygen supply to the potentially infarcted zone is 3 per cent of the normal. After the above outlined surgical procedure the potential supply would be increased to about 7 per cent of the normal requirement. When we study the
over all picture we are impressed by the narrow margin between life and death in an acute coronary arterial occlusion, and how important it is that a little blood continue to flow into the ischemic myocardium. The fact that infarction is significantly reduced is ample proof that the increase in collateral flow as observed in the backflow studies provides for sufficient flow in the myocardial capillaries to maintain the viability of muscle fibers that would otherwise undergo necrosis. This represents one of the ultimate tests of benefit that can be applied to the procedure.

Thompson has advocated a procedure first suggested by Beck in 1936 of simple pericardiotomy and introduction of a powdered foreign body irritant into the pericardium. Beck used powdered beef bone and Thompson has used powdered magnesium silicate (U.S.P. Talc). Backflow studies after the Thompson procedure have shown a slight increase in average backflow but considerably less than the combined procedure described above. However, Thompson et al have reported good clinical results from this procedure in a rather large series of patients.

To date there is no crucial laboratory data on the effectiveness of the combined stimulus provided by the surgical procedure plus the simultaneous factor of chronic narrowing of the coronary arteries. The fact that the clinical results seem better than one might expect from the study of the relatively acute backflow experiments suggests that the benefit to collateral blood flow may be magnified by an already existing reduction in arterial inflow.

8. Metabolic Factors Operative in the Augmentation of Collateral Coronary Circulation

The studies that have been discussed naturally arouse curiosity concerning the fundamental biological factors that cause interarterial anastomoses to enlarge. It has been common to employ the teleological assumption that a need for blood stimulates the enlargement of collateral channels. Although this might be true in a sense it should be possible to identify the factors be they physical or metabolic responsible for the vascular architectural change that lead to this rather enormous enlargement of collateral channels.

Wiggers has emphasized the possible importance of a differential of pressure between arteries as a stimulus to collateral development. In our previously reported studies there were two instances in which there was complete infarction of the parts of the wall of the right ventricle supplied by the acutely occluded right coronary artery with conversion into scar tissue. Although the right coronary artery was in each case patent distal to the occlusion, the backflow and peripheral coronary pressure in one were exceedingly low, the backflow being 0.1 cc./minute. Significant enlargement of intercoronary anastomoses was absent in both by injection studies. In these instances in spite of a wide differential of pressure existing for many months no enlargement of collateral channels had taken place. Indeed, such a finding is perfectly reasonable since the metabolic requirements of scar tissue must be much lower than functioning myocardium. It
is believed and has been previously suggested\textsuperscript{17, 54} that factors within an ischemic zone of myocardium influence blood flow into the ischemic zone perhaps first by a reversible pharmacological dilation of anastomoses which lowers resistance to flow and that the subsequent permanent anatomical enlargement of the collateral channels may be secondary to the physical effects of flow within the collateral rather than the mere pressure differential. In the earlier reported studies of the development of intercoronary collateral following chronic arterial occlusion,\textsuperscript{17} treadmill exercise was given to some of the animals with constriction of coronary arteries with the belief that increased work of a segment of myocardium distal to a narrowed artery would be the physiological equivalent of temporarily increasing the degree of ischemia distal to the arterial narrowing and that this would serve as an added stimulus to the further development of collaterals. The collateral enlargements were successfully produced but the specific role of the exercise was not determined in these studies. More recently, using the same treadmill, Eckstein\textsuperscript{55} has shown that when dogs with narrowing of a coronary artery are exercised they develop significantly more collateral than control animals that receive no exercise. Further studies into the chemistry and pharmacology of inflammation and of myocardial hypoxia may further elucidate and explain specific mechanisms involved. The findings of Zoll et al\textsuperscript{56} and others\textsuperscript{56, 57} of enlargement of intercoronary anastomoses in the absence of coronary arterial disease in chronic anemia, valvular disease, cardiac hypertrophy and cor pulmonale with pulmonary fibrosis fits well into such a concept. Eckstein\textsuperscript{56} has shown that the enlargement of intercoronary channels that occurs during four weeks of severe anemia in experimental animals disappears following correction of the anemia, being yet in the reversible phase. It is probable that this represents principally the pharmacological effect of metabolites and that if the anemia were sufficiently prolonged that permanent anatomical changes would take place that would not be reversible.

**SUMMARY AND CONCLUSIONS**

The anastomoses between coronary arteries present in the normal heart provide a basic collateral circulation, which while not sufficient to maintain myocardial contractions following acute interruption of the normal arterial supply, generally enables the survival of variable amounts of myocardium providing death of the individual does not follow the occlusion. In the survivors there is a gradual enlargement of collateral circulation quite variable in amount but sufficient to enable the ischemic myocardium to again regain its contractile ability. The collateral blood comes exclusively from other arteries. The nearest artery or the anatomically shortest path of least resistance appears to be the commonest source and route. In the early phase of the reduction of coronary arterial inflow the majority of the collateral is supplied by other coronary arteries. If and when it is possible to reduplicate the experiments of nature and completely interrupt all the normal arterial inflow to the myocardium with survival, it should be possible to trace and measure the blood flow from the extracardiac arterial sources.
The surgical procedure of abrasion of the epicardium, coronary sinus constriction and the application of a mild chronic chemical irritant (powdered asbestos) to the heart significantly increases the basic collateral circulation available to the myocardium. This increase in basic available collateral has been noted to persist for at least one year and has been shown to significantly lower the mortality and myocardial destruction following acute arterial occlusion.

The exploration of the application of these principles in the treatment of coronary disease in man would appear to be axiomatic. The principle of improving the collateral circulation to the myocardium must be the sine qua non of our search for a better treatment of coronary disease until such time as the arteriosclerotic process can be prevented or arrested.

The ultimate precise measure of benefit in man will depend upon the comparison of similar groups of treated and untreated patients with disease of the coronary arteries. In spite of pessimism such as has been voiced by Blumgart and Paul,1a to find an answer to the question of benefit in man should not be exceedingly difficult for good clinicians who view the biological problem objectively. A careful plan of preoperative study of patients and an adequate system of follow-up will in time yield a precise answer. No doubt much is yet to be learned but the evidence at hand indicates that a firm foundation has been established for improving collateral circulation to the myocardium by surgical methods.

RESUMEN Y CONCLUSIONES

Las anastomosis entre las arterias coronarias que existen en el corazón normal proporcionan una circulación colateral básica que sí bien es insuficiente para mantener las contracciones cardiacas después de una repentina interrupción del aporte sanguíneo normal, generalmente permite la sobreviva de variables volúmenes del miocardio cuando la oclusión no es seguida de muerte inmediata.

En los supervivientes hay un gradual aumento de la circulación colateral muy variable en volumen pero suficiente para permitir que el miocardio isquémico recupere su contractibilidad. La sangre colateral viene exclusivamente de otras arterias.

La arteria más próxima o la senda anatómica más corta y de menor resistencia parece ser la fuente provisora. En la fase temprana de la reducción del aflujo sanguíneo la mayoría de la sangre es proporcionada por las otras coronarias. Cuando sea posible imitar la experiencia e interrumpir completamente todo el aflujo sanguíneo arterial normal del miocardio con sobreviva, será posible estimar y calcular el aflujo sanguíneo que provenga de fuentes arteriales extracardiacas.

El procedimiento quirúrgico consistente en la abrasión del epicardio, la constricción del seno coronario y la aplicación de irritantes químicos moderados (polvo de asbesto) al corazón aumenta el aporte sanguíneo colateral del miocardio. Se ha notado que este aumento circulatorio persiste por lo menos un año y ha hecho descender notablemente la mortalidad y el daño al miocardio después de la oclusión arterial.
La exploración de la aplicabilidad de estos principios en el tratamiento de la enfermedad coronaria en el hombre parecería axiomática.

Hasta que el proceso arterioescleroso pueda ser evitado o detenido es preciso buscar los métodos que mejoren la circulación del miocardio. La estimación del valor de los métodos depende de la comparación de grupos tratados y no tratados. A pesar del pesimismo mostrado por Blumgart y Paul (58) no es difícil llegar a una respuesta si los buenos clínicos observan el problema biológico objetivamente.

La observación previa y posterior a la cirugía rendirán una respuesta precisa. No hay duda que falta mucho por lograrse para mejorar la circulación colateral del miocardio.

RESUME

Les anastomoses entre artères coronaires dans le coeur normal permettent une circulation collatérale de base. Elle est insuffisante à maintenir les contractions myocardiques à la suite de l'interruption brutale du débit artériel normal. Toutefois, elle permet généralement la survie d'un territoire variable du myocarde, si la mort n'a pas immédiatement fait suite à l'occlusion. Chez les survivants, il y un accroissement progressif de la circulation collatérale, assez variable en quantité, mais suffisante pour permettre au myocarde ischémique de retrouver sa capacité contractile. Le sang collatéral vient exclusivement des autres artères. L'artère la plus proche ou la voie anatomiquement la plus courte et où il y a le minimum de résistance en sont l'origine la plus commune.

Dans la phase précoce de réduction du débit artériel coronaire, la plus grande partie de la circulation collatérale est fournie par les autres artères coronaires. Quand il sera possible de reconstituer l'expérience que nous offre la nature, en interrompant complètement tous les apports normaux de sang artériel au myocarde, tout en maintenant la survie, on devrait arriver alors à mesurer le débit sanguin à partir de ses sources artérielles extracardiaques.

Le procédé chirurgical de l'abrasion de l'épicarde, la constriction du sinus coronarian, et l'application sur le coeur d'un irritant chimique permanent à action douce (amiante en poudre) accroît considérablement la circulation collatérale destinée au myocarde. On a noté que cette augmentation persistait pendant au moins un an, et permettait une diminution considérable de la mortalité et de la lésion myocardique consécutive à l'occlusion artérielle aiguë.

L'application de ces principes au traitement des affections coronariennes chez l'homme devrait se présenter comme un axiome. L'amélioration de la circulation collatérale du myocarde doit être l'élément "sine qua non" de nos recherches sur le traitement de l'infarctus du myocarde tant que nous ne serons pas arrivés à éviter ou à freiner le processus d'artériosclérose.

Le seul moyen précis d'en mesurer l'avantage chez l'homme consistera à comparer des groupes semblables de malades atteints d'affections coronariennes, les uns ayant subi le traitement, les autres ne l'ayant pas subi.
Malgré le pessimisme de Blungart et Paul, une réponse à la question de savoir si un tel procédé est avantageux pour l'homme ne devrait pas comporter de difficultés excessives pour de bons cliniciens qui voient objective-
ment le problème biologique. Un plan soigneux d'études pré-opératoires des malades, et un système convenable de contrôle doit fournir une réponse en temps voulu. Il n'y a aucun doute qu'il reste beaucoup à apprendre, mais nous avons la certitude de posséder une base solide qui nous permet d'amé-
lìorier les troubles de la circulation collatérale par des procédés chirurgi-
caux.

ZUSAMMENFASSUNG UND SCHLUSSFOLGERUNGEN

Die im normalen Herzen bestehenden Anastomosen zwischen Koronar-
erien gewährleisten die Basis eines collateralen Kreislaufes, der—ob-
wohl nicht ausreichend für die Aufrechterhaltung von Herzmußkel-Kon-
traktionen nach akuter Unterbrechung des normalen ateriellen Zuflusses-
im allgemeinen das Überleben variabler Teilstücke des Myocards ermög-
lichen, sofern der Tod des Individuums nicht auf den Verschluss folgt.

Bei dem Überlebenden kommt es zu einer schrittweisen Zunahme der col-
lateralen Zirkulation, die in ihrer Stärke ziemlich schwankt, aber aus-
reicht, um dem ischämischen Myocard zu ermöglichen, sein kontraktiler
Vermögen wieder zu gewinnen.

Das kollaterale Blut stammt ausschließlich aus anderen Arterien. Die
nächstgelegene Arterie oder der anatomisch kürzeste Weg des geringsten
Widerstandes dürfte für gewöhnlich der Ursprung und der Verlauf sein.

Während der ersten Phase der Herabsetzung des Koronarerien-Zu-
stromes wird die Mehrzahl der Kollateralen durch andere Koronarerien
versorgt.

Im Falle es möglich wäre, die Experimente der Natur zu wiederholen
und den gesamten normalen ateriellen Zufluss zum Myocard vollständig
to unterbrechen, ohne dass der Tod eintritt, müsste es auch möglich sein,
den Blutstrom extracardialer arterieller Herkunft zu verfolgen und zu
messen.

Das chirurgische Verfahren der Epicard-Abrasio, Verengung des sinus
coronarius und der Gebrauch eines milden chronischen chemischen Reiz-
mittels—Abest-Puder—verbreitert die Basis für den dem Myocard zur
Verfügung stehenden Collateral-Kreislauf beträchtlich. Es wurde beob-
achtet, dass diese Verbreiterung der Basis der zur Verfügung stehenden
Kollateralen mindestens 1 Jahr anhält, und es wurde gezeigt, dass die
Mortalität und die Zerstörung des Myocards nach akutem arteriellem Ver-
schluss beträchtlich verringert wurde.

Die Erforschung der Anwendung dieser Grundsätze bei der Behandlung
von Koronarerkrankungen beim Menschen erscheint axiomatisch. Das
Prinzip der Verbesserung der collateralen Zirkulation für das Myocard
muss so lange die conditio sine qua non unseres Bestrebens nach einer
besseren Behandlung der Koronarerkrankungen sein, bis der ateriosklero-
tische Prozess verhütet oder zu Stillstand gebracht werden kann.

Der am Ende genaueste Massstab eines Nutzens für den Menschen wird
abhängen von dem Vergleich ähnlicher Gruppen von Behandelten und nicht

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