Stimulation of Interarterial Coronary Anastomoses by Experimental Acute Coronary Occlusion

By Milton H. Paul, M.D., Leona R. Norman, M.D., Paul M. Zoll, M.D., and Herrman L. Blumgart, M.D.

"Hence it sometimes happens that, when the lumen of some artery has been too long obstructed or ligated, the blood busies itself in opening a wider channel for its passage in this vessel, must drive and buffet all the more into the next ones, until it has considerably dilated them to give itself room." [1]

The development of interarterial coronary anastomoses may exert a profound influence on the clinical course of angina pectoris, coronary failure, and acute myocardial infarction. Earlier studies have shown that marked narrowing of a coronary artery produces rich intercoronary anastomotic communications. The present study is designed to determine whether acute occlusion of a coronary artery in a previously normal heart also leads to the development of a collateral circulation and what length of time is necessary to establish such a collateral circulation.

Following acute coronary occlusion, the infarcted myocardium is bordered by a zone of injured tissue that may undergo either necrosis or recovery. Bed rest or marked restriction of effort is prescribed after acute myocardial infarction to reduce the work of the heart, to minimize the size of the infarct, to favor recovery of the injured myocardial tissue, and to lessen the liability of cardiac rupture, congestive heart failure, and arrhythmia. According to previous experimental studies in the domestic pig, [2-4] 12 or more days of 75 per cent narrowing are required to produce sufficiently rich intercoronary anastomotic communications to protect the myocardium from damage and to permit survival when the coronary circulation is subsequently challenged with an acute complete occlusion.

The present study was undertaken to learn (1) whether acute occlusion of a coronary artery in a previously normal heart leads to the development of a collateral circulation, just as marked narrowing does, and (2) the length of time necessary to establish such a collateral circulation.

Methods

As in the previous studies on the effect of acute narrowing on the production of larger intercoronary collateral channels, the domestic pig was chosen as the experimental animal because pig hearts ordinarily do not show interarterial coronary anastomoses when injected with lead-agar mass. [2-4] In the normal dog, grossly visible interarterial communications, 100 microns or larger in diameter, were often demonstrated by this injection technic. [3-5]

Experimental Technic

Young pigs weighing 5 to 10 Kg. received 0.5 mg. of atropine sulfate preoperatively. Endotracheal ether anesthesia was employed. The heart was exposed by an incision through the third or fourth left intercostal space and the pericardium was opened. The left circumflex artery or one of its primary branches (table 1) was carefully dissected from its bed and a double ligature was passed around it and tied. Our previous studies in the pig demonstrated that acute occlusion of any of the 3 main coronary arteries near their origin uniformly resulted in death. [3-4] In all the experiments of the present study, therefore, the left circumflex artery near its termination or one of its larger primary branches was selected for ligation. After various intervals (table 1) the pigs were sacrificed and the coronary arteries were examined post mortem with the injection plus dissection technic. The left anterior descending, the left circumflex, and the right coronary arteries were each individually cannulated via the aortic coronary ostia. The usual lead-agar mass was used—colored blue for the left descending, red for the right coronary, and yellow for the left circumflex coronary arteries. In order to fill any interarterial communications more completely, the technic of

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Table 1.—Extent of Anastomosis after Ligation of Left Circumflex Coronary Artery

<table>
<thead>
<tr>
<th>No.</th>
<th>Main stem or branch</th>
<th>Survival after ligation (days)</th>
<th>Anastomosis*</th>
<th>Infarction</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>1†</td>
<td>0</td>
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<td>2</td>
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<td>3</td>
<td>B</td>
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<tr>
<td>23</td>
<td>M</td>
<td>29</td>
<td>1+</td>
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M = main stem of left circumflex coronary artery near terminal end.
B = branch of left circumflex coronary artery near terminal end.
* Anastomosis is graded from 0 to 3+.
† Hours.

Injection was slightly modified by application of positive and negative pressures of 150 mm. Hg to the 3 cannuas in all possible combinations, with final application of positive pressure. The injection mass introduced in this manner into each of the 3 major coronary arteries in the hearts of normal pigs has previously been shown uniformly not to fill the smaller arteriolar vessels between 10 and 50 μ in diameter, and not to reach the capillary bed or the venous tree at all.2−6

RESULTS

Normal and Control Groups

In 158 of 161 normal pig hearts no interarterial coronary anastomotic connections were found. In 2 hearts superficial anastomosing twigs were faintly outlined with injection mass; in only 1 normal control heart was there abundant intercoronary anastomosis such as seen after marked narrowing or complete occlusion (see below). Thus, the natural or spontaneous incidence of anastomoses of any degree in this series is 2 per cent.

In a second group of surgical control experiments 17 pigs underwent anesthesia or surgery but did or were sacrificed within 24 hours of the surgical procedure. In 11 instances the vessel was not tied or the animal did not survive the ligation. In 6 of the animals ligation of the left circumflex coronary artery was accomplished; however, since the animals died within 1 to 24 hours of ligation, they are included in this control group. These 6 animals also are listed in the table among the 23 animals in whom the left circumflex coronary artery was ligated (nos. 1 to 6, table 1). Slight anastomoses (1+) were found in only 1 of these 17 animals. Figure 1 shows the usual pattern of absent anastomosis in a control animal that died 4 hours after the left circumflex coronary artery was ligated; the peripheral segment of the vessel remained uninjected.

Intercoronary Anastomoses after Acute Coronary Arterial Occlusion

The table lists 23 animals that survived acute ligation of the left circumflex coronary artery. Of 17 animals who survived from 2 to 29 days after acute occlusion (nos. 7 to 23, table 1), abundant collateral circulation was observed in 13 (77 per cent). The segments of left circumflex coronary artery distal to the occlusion were filled with mass by way of interarterial anastomoses from the right coronary artery, the left anterior descending, or the left circumflex artery proximal to the tie. These anastomoses did not develop indiscriminately or diffusely in the coronary tree but in general bordered the infarcted area. The occurrence of extensive anastomoses in 77 per cent of the hearts in this group differs significantly from the incidence of slight anastomosis of only 2 per cent in the hearts from normal control pigs and from those surviving less than 2 days. Figure 2 shows rich anastomoses in the peripheral segment of the left circumflex artery (graded 3+) in a pig that was sacrificed 4 days after coronary artery ligation. In 3 animals surviving 7, 11, and 17 days (no. 11, 14, and 16...
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Fig. 1. Roentgenogram of injected and unrolled heart of pig no. 2 that died 4 hours after ligation of the left circumflex coronary artery. The peripheral portion of the vessel is uninjected (0 anastomoses). The arrow shows the point of ligation of the left circumflex coronary artery.

respectively) after occlusion, anastomotic channels were absent; the explanation for this failure of anastomosis to develop is not clear. We are not cognizant of an error in the technic of coronary artery ligation or faulty postmortem injection of these hearts. One can only conjecture that occasionally the area of infarction by chance completely involves all those vessels that provide the source for the development of such intercommunications. Such occasional exceptions occurred in previous similar studies by us\textsuperscript{3, 4} and others.\textsuperscript{7, 8} It is to be noted also that there was no apparent relation between the length of survival after occlusion and the abundance of the anastomotic channels. Thus, in 2 animals surviving 18 and 29 days, the extent of the anastomoses was moderate and slight (fig. 3), respectively, whereas in animals no. 8 and 10, who survived 2 and 4 days (fig. 2), the anastomoses were marked.

DISCUSSION

The results of the present study are in harmony with our previous observations regarding the characteristics of intercoronary communications. In the normal heart of the pig, dog, and man, fine interarterial coronary communications may be demonstrated by the ready passage of colored watery solutions or suspensions like India ink from one coronary artery to the other coronary arteries and their branches. These normal, anatomically demonstrable communications do not protect the myocardium from infarction when a coronary artery is occluded suddenly. They are therefore not of important functional significance, and the coronary arterial system may be regarded in these 3 species as an end-arterial system from the functional or physiologic standpoint.\textsuperscript{8, 9} Larger interarterial communications, which are demonstrable by the Schlesinger technic, are present in 9 per cent of normal human hearts from patients without anemia.\textsuperscript{6} In the pig, however, only 3 of 161 hearts examined have shown anastomoses; in 2, they were very slight. We can therefore be confident that the anastomoses observed in the present study
Fig. 2 Top. Roentgenogram of injected and unrolled heart of pig no. 10 that was sacrificed 4 days after ligation of the left circumflex coronary artery. The site of ligation (arrow) is well seen as an interruption of the injection mass, which fills the peripheral portion of the vessel by rich collateral vessels (3+ anastomosis) below the black rod.

Fig. 3 Bottom. Roentgenogram of injected and unrolled heart of pig no. 23 that was sacrificed 29 days after ligation of the left circumflex coronary artery (arrow). Only slight filling of some terminal twigs of the left circumflex artery was found on dissection (1+ anastomosis) and is seen on the film just below the black rod.
were not normally present and were consequent to the experimental procedure.

These intercoronary arterial anastomoses have engaged the interest of investigators because of their important function, after marked narrowing or complete occlusion of a coronary artery, in supplying blood from neighboring arteries to the capillaries and tissues of an infarcted or potentially infarcted area. The classic observations of Gregg and his associates\(^{10-12}\) demonstrated that the blood delivered through these channels is arterial in nature and derived from the intact coronary arteries. Indeed complete occlusion of a main coronary artery gradually accomplished in successive stages was often not accompanied by myocardial infarction in the dog. Similar experimental observations were made by Blum, Schauer, and Calef,\(^{13}\) by Burchell,\(^{14}\) and by us.\(^3\)

The clinical counterpart of these experiences, i.e., the occurrence of complete coronary artery occlusions without myocardial infarction, has been noted by Saphir and his associates,\(^{15}\) by Bean,\(^{16}\) and by ourselves.\(^6\) Recently, however, Snow, Jones, and Daber\(^7\) have questioned the efficacy of the collateral vessels in preventing myocardial necrosis completely. They always found gross myocardial infarction of some extent in association with occlusions, although often considerably smaller than might otherwise have been expected. Since their observations were made in a series of 25 patients limited to those with clinical manifestations of coronary disease, instances of complete protection from infarction may well have been eliminated from consideration at the outset by the method of selection. In any event there is no question about the development of intercoronary anastomoses and their importance in ameliorating the consequences of coronary artery occlusion.

In the present study, as in our other studies, the injection mass never traversed pericardial adhesions to adjacent structures such as the venae cavae, the aorta, the pulmonary vessels, and the reflections of the parietal pericardium, despite the presence of fine extracardiac communications vessels that may be demonstrated anatomically by the injection of india ink or similar suspensions. Similarly, if coronary-luminal communications of smaller size are present, they are like the normal fine interarterial coronary and extracardiac communications in that they are of little functional significance in safeguarding the myocardium after acute coronary occlusion.

Our previous studies showed early development of collateral circulation within 2 days in response to marked narrowing, but 12 or more days were generally necessary for the evolution of a rich anastomotic circulation that was functionally adequate to protect the heart from sudden, superimposed complete occlusion.\(^3\),\(^4\)

The interval of 2 days required for the development of anastomoses in the present studies of occlusion is compatible with the previous observations after narrowing.

Although the results of this study demonstrate conclusively that increased collateral channels develop between unoccluded arteries and the occluded segment of another artery within 2 days, one cannot conclude that the collateral channels have reached their maximum development by that time. Donald and Essex,\(^7\) using a barium-gelatin mixture to inject the dog heart after gradual occlusion of the right coronary artery close to the aorta, found that a postligation period of over 3 weeks was necessary for the evolution of a rich anastomotic circulation. Incomplete filling of the occluded artery was found in hearts examined after injection of the barium-gelatin material 1, 4, 9, 14 and 22 days after ligation of the right coronary artery at its origin. The longer time required for demonstration of collateral channels in their experiments may be due to differences in the injection mass, the site of the arterial ligation, species differences, and different criteria for demonstration of anastomotic injection in the 2 studies. It was shown by pathologic examination of the heart that sufficient retrograde flow occurred early to save some of the myocardium from necrosis.

The technic used in the present study of complete nonlethal ligation of a small branch of a coronary artery is better suited to the study of effects of drugs and various agents upon the development of intercoronary anastomoses than the technic of marked narrowing of a large vessel with subsequent ligation. It is
simpler and easier technically, obviates the major variable that is difficult to control (degrees of narrowing), and gives a higher per cent of control figures for comparison.

The relations of angina pectoris, coronary failure, and acute myocardial infarction to coronary arterial narrowing and occlusion and the development of collateral vessels in human hearts have been the subject of previous communications by us. We have reviewed our series of human hearts injected by the Schlesinger injection plus dissection method but have not found any exact clinical counterpart of the above described experimental situation: we have found no instance in which an acute coronary occlusion occurred in the presence of an otherwise normal coronary arterial tree; in every instance areas of moderate or marked narrowing were evident in other areas of the coronary arterial tree. Thus we are unable directly to extend these experimental findings with the present clinical autopsy material of more than 1000 hearts. Nevertheless, the observations of the present study in the uncomplicated experimental situation are valuable for orientation in clinical cases where acute complete occlusion occurs in hearts with varying degrees of narrowing.

In coronary artery disease extensive narrowing of the coronary arterial tree might preclude the development of a steep pressure gradient between neighboring uninvolved vessels. The derivation of collateral blood supply from such arteries following acute coronary occlusion in the human heart might then be expected to require a somewhat longer interval than the 2 or more days of the present experimental study. Moreover, the occasional heart observed in this and other series of animals in which much longer times are necessary to establish a rich collateral blood supply emphasizes the importance of bed rest and reduced activity for many weeks after acute myocardial infarction.

**Summary**

In a control series of 161 normal pig hearts only 3 hearts (2 per cent) were found to have intercoronary anastomotic connections by a technic of injection plus dissection of the coronary arteries with lead-agar mass.

In contrast, of 17 animals who survived from 2 to 29 days after acute coronary occlusion, abundant collateral circulation was observed in 13 (77 per cent).

These studies indicate that a significant intercoronary collateral circulation can develop within 2 days after acute coronary ligation.

**SUMMARIO IN INTERLINGUA**

In un serie de controlo de 161 normal cordes porcin solmente 3 (2 pro cento) revelava le presentia de anastomotic connexiones intercoronari. Le technica usate essueva dissection post injection de un massa de agar a plumbo in le arterias coronari.

Del alteare lateré, inter 17 animales supervivente 2 a 29 dies post acute oclusión coronari, 13 (77 pro cento) monstrava un abundante circulation collateral.

Iste studios prova que un significative circulation collateral intercoronari pote desenvoloppar se intra 2 dies post acute ligation coronari.

**REFERENCES**

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A great discovery is not a terminus, but an avenue leading to regions hitherto unknown. We climb to the top of the peak and find that it reveals to us another higher than any we have yet seen, and so it goes on.—George Thomson. Centenary of J. J. Thomson. Science 124: 1195, 1956.
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