Regression and reappearance of coronary collaterals

EDWARD M. KHOURI, DONALD E. GREGG, AND GEORGE M. MCGRANAHAN, JR.
Department of Cardiorespiratory Diseases, Walter Reed Army Institute of Research,
Walter Reed Army Medical Center, Washington, D. C. 20012

Khouri, Edward M., Donald E. Gregg, and George M. McGranahan, Jr. Regression and reappearance of coronary collaterals. Am. J. Physiol. 220(3): 655-661. 1971.—The regression of the coronary collateral circulation after an occlusion is removed and its ability to develop again following reocclusion was studied in two groups of dogs. In one group the first occlusion of the circumflex branch of the left coronary artery was gradual, and only transient myocardial ischemia was evidenced; in the other it was abrupt, resulting in massive infarction. In both groups, following the initial occlusion, the collateral indices increased, and after 1-6 days the left descending coronary flow had nearly doubled and circumflex peripheral pressure had reached 40-72 mm Hg from a control of 10-24 mm Hg. The occlusion was then released. Left descending coronary flow and circumflex peripheral pressure dropped and equilibrated to near-control levels in 3 hr-1 day. Following reocclusion of the circumflex 3-90 days later, the collateral indices rose within 1 hr to the levels obtained on the 1st to 6th day after the initial occlusion. Essentially no myocardial damage was seen following the gradual occlusions. The results suggest that coronary collaterals become nonfunctional when the need for them is removed, but remain ready to resupply the myocardium within a very short time following a subsequent occlusion.

coronary occlusions; collateral regression; collateral indices; retrograde flow; peripheral coronary pressure; electromagnetic flowmeter

Although numerous studies have been made of coronary insufficiency (1, 2, 5, 6, 9, 10, 12) and have shown the development and functioning of the collateral circulation, little, if any, work has explored what happens to these collaterals after an occlusion is removed. In none of these experiments was it possible to control the closure and release of the occlusion in the unanesthetized animal. The use of a constrictor which can be controlled externally and which was first screened electrocardiographically to eliminate those with evidence of past myocardial involvement and then trained to lie quietly at rest on a padded table for periods of 4 hr or longer. The preparation shown schematically in Fig. 1 is essentially similar to that previously reported (5, 8). Flow in the circumflex and descending branches of the left coronary artery was measured with electromagnetic flowmeters positioned as close to their origins as possible. Zero flow was obtained by inflating pneumatic occlusive cuffs implanted immediately distal to the flow transducers and separated from them by a 2 to 3-mm bridge of Ivalon sponge. Coronary occlusion, either gradual or abrupt, was induced and maintained by a special hydraulic occlusive device (8) on the circumflex branch, distal to the zero cuff. Indwelling catheters in the ascending aorta and the circumflex branch were used to measure central aortic blood pressure and circumflex peripheral coronary pressure, i.e., the residual pressure beyond the point of coronary occlusion. These catheters were similar to that described by Herd and Barger (7), except that the intravascular portion was made of medical grade silastic tubing. Figure 2 shows the technique used to attach the silastic portion of the catheter to the polyvinyl chloride tubing and the curved hypodermic needle shaft. A special transcutaneous sliding obturator valve was used to close the coronary artery catheter and is also shown in Fig. 2. Generally, blood flowed freely each time the valve was opened; very rarely was it necessary to inject saline first into the tube or to administer a fibrinolytic agent. Both pressure catheters were flushed once a day with saline, then filled with a heparin solution, 10 mg/ml for the aortic and 200 mg/ml for the intracoronary catheter. Phasic aortic and circumflex pressures were measured with Statham P23gb transducers; pressure and flow records were obtained on an Electronics for Medicine DR-8 recorder or a Hewlett-Packard 350 system feeding a Honeywell 1912 recorder. Standard ECG leads were also monitored and recorded periodically.

A period of 7-12 days was allowed for recovery from surgery. Then, following 4-7 days of control studies, circumflex insufficiency was initiated in either of two ways. In one group of dogs, the first circumflex occlusion was gradual, zero flow being reached within a period of 3-12 days. In the other group, it was abrupt and total. In both groups, 1-6 days after establishment of zero flow, the occlusion was released and the measured parameters were allowed to equilibrate over a period of days to months. The circumflex branch was then reoccluded for 8 min to 2 hr. All reocclusions were abrupt; most of the dogs were subjected to more than one reocclusion.

During the progressive partial circumflex occlusion, the
results

Twelve dogs were prepared for this study. Three died 1–4 days after surgery of pulmonary difficulties. In one, flow could not be re-established in the circumflex branch because of a thrombus at the level of the flow transducer; in another the occlusive device failed 8 hr after the first occlusion. In four of the seven dogs reported here, the first circumflex occlusion was gradual; in the other three it was abrupt. One died of unknown causes 4 days after release of the second occlusion. Retrograde flow was measured in four of the remaining six dogs. Because of anatomical limitations in some dogs, all the coronary devices were not installed in every dog. Five were fitted with only the systems on the circumflex branch, one was equipped with all but the intracoronary catheter, one was complete as shown in Fig. 1. The results are illustrated in Figs. 3 and 4 and Table 1.

Figure 3 (dog 2) shows the responses to a progressive partial coronary occlusion over 5 days, total coronary occlusion for 3 days, release of the occlusion, and 5 days later reocclusion for 60 min. The results of a partial occlusion gradually progressing to a complete cessation of flow have been reported previously (5, 6). Briefly, as the partial circumflex occlusion progresses, resting flow in that vessel remains unchanged until the hyperemic response to a temporary occlusion disappears. Up to that point, the resting left descending coronary flow changes very little, but its peak hyperemic response increases slightly; circumflex peripheral coronary pressure also increases mildly. During the subsequent 3 days of total circumflex occlusion, left descending coronary flow increases to 40 ml/min from a control of 24, and its peak reactive hyperemia response rises to 190 ml/min from a control of 116; circumflex peripheral coronary pressure increases from 15 to 62 mm Hg. At this time, temporary closures of the descending branch resulted in the circumflex peripheral coronary pressure dropping from about 62 to 30 mm Hg (arrows to open circles). Throughout the progress in occlusion, the ECG showed only slight transient changes in the ST-T segment, heart rate and arterial blood pressure were not grossly affected.

Three days after total occlusion was achieved, the circumflex constriction was removed completely. At the end of the 5–7 sec necessary to release the constritor, circumflex flow had stabilized at the control level; no reactive hyperemia was seen. The circumflex reactive hyperemia response, negligible at first, returned rapidly and could be detected 2 min after the release. Left descending coronary flow dropped almost immediately to near-control level and its peak reactive hyperemia response decreased gradually. Circumflex peripheral pressure dropped immediately from 62 to 40 mm Hg, then within hours returned to control values. During the short occlusions necessary to measure circumflex peripheral pressure and hyperemic response, the left descending coronary flow, at first, increased considerably (from 20 to 43 ml/min); this increase gradually became smaller (open circles and shaded area). Three hours after the release, the increase in descending flow during short temporary circumflex occlusions was no longer apparent, peak circumflex hy-
coronary collateral regression

Fig. 2. Top left: coronary pressure catheter. 1: one end of silastic tubing (0.012 inch id x 0.025 inch od) enlarged by soaking in ether is slipped over a 3-mm length of 21-gauge thin-wall needle stock. Polyvinyl chloride tubing (0.018 inch id x 0.030 inch od) is then stretched over silastic covered needle length. 2: grooved 1-mm length of 19-gauge thin-wall needle stock cemented over silastic tubing with silastic medical adhesive type A and used to support a ligature. 3: 2-cm length of 0.012-inch stainless steel wire attached in lumen of curved needle shaft with solder or epoxy resin and to silastic tubing with silastic adhesive. Stabilizing ligatures (shown) are cemented over the PVC tubing with vinyl cement. Aortic catheter is made similarly, except that 0.032 inch id x 0.042 inch od silastic and 0.038 inch id x 0.072 inch od vinyl tubings are used with appropriately larger steel hardware. Top right: cross-sectional drawing of sliding obturator valve. Bottom: modified forceps used to open and close valve.

pericmic response had nearly reached the preocclusion level of 120 ml/min, while the peak descending hyperemic response had returned to 117 ml/min. The circumflex peripheral pressure was also back to the control level of 15 mm Hg.

Five days after the release the circumflex was again occluded, this time abruptly and totally. The ECG showed no change; heart rate and arterial blood pressure remained within the normal moment-to-moment variations; left descending coronary flow and circumflex peripheral pressure increased steadily and rapidly. One hour after the reocclusion left descending coronary flow had reached 40 ml/min and circumflex peripheral pressure was up to 60 mm Hg. In contrast, these high values were not reached until 1 day following the first total occlusion, even though that initial occlusion was preceded by 5 days of partial occlusion.

Similar systemic and coronary responses were observed in dogs 1, 3, and 4 (Table 1) in which the circumflex flow was gradually reduced to zero. Dog 1 had two reocclusions 15 and 25 days apart. The circumflex peripheral pressure was not measured, but the left descending coronary flow increased from 32 to 60 ml/min in only 8 min, whereas following the first occlusion (12 days partial and 6 days total) it had risen from 24 to 55 ml/min. In dog 3 one reclosure was performed 7 days after release of the first occlusion, and the circumflex peripheral pressure rose from 23 to 57 mm Hg within 1 hr, compared to an increase from 24 to 72 mm Hg after 3 days of partial and 3 days of total first occlusion. In dog 4 two reclosures were done at intervals of 30 days. The first resulted in a peripheral circumflex pressure increase from 14 to 44 mm Hg in 2 hr, compared to an increase from 13 to 47 mm Hg following 3 days of partial and 1 day of total initial occlusion. The second reclosure was done under anesthesia and is reported below.

Circumflex retrograde flow measurements were also made in dogs 3 and 4, after the circumflex had been opened for 7 and 30 days, respectively. In the first dog the artery was reclosed at the time anesthesia was given and the retrograde flow collections were made about 1 hr after reclosure; the measured backflows averaged 37 ml/min.
**TABLE 1. Summary of data**

<table>
<thead>
<tr>
<th>Dog</th>
<th>Control</th>
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<th>Reocclusions</th>
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<td>6</td>
<td>55</td>
<td>10</td>
<td>Abrupt</td>
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In dog 4 reocclusion occurred during cannulation of the circumflex, and repeated backflow collections were made starting about 1.5 min later. The early collection was 12 ml/min; the backflow increased rapidly and 30 min later was 20 ml/min.

Figure 4 (dog 5) illustrates the results of a total and abrupt occlusion maintained for 4 days, release of the occlusion, and 11 days later reocclusion of the circumflex branch. The pattern of response to the initial acute occlusion for the first 24–30 hr has been reported previously (11). Initially, sinus rhythm was retained, heart rate and arterial blood pressure rose, and circumflex peripheral pressure tended to follow. In 3–9 hr there were many ventricular beats, and in 24 hr the rhythm was entirely ventricular with marked elevation of arterial blood pressure and circumflex peripheral pressure. In about 2 days, a
few sinus beats could be observed, and although the heart rate remained high, arterial blood pressure and circumflex peripheral pressure dropped slightly. The stabilization trend continued and on the 4th day following occlusion, the heart was in normal rhythm with distinct sinus arrhythmia; the heart rate of 62 and the arterial blood pressure of 85 mm Hg matched the control values before occlusion. Despite the lowered heart rate and blood pressure, circumflex peripheral pressure remained high at 49-50 mm Hg and was still increasing.

The occlusion was then released. Heart rate and arterial blood pressure remained within the spontaneous fluctuations normal to the unanesthetized animal; left circumflex coronary flow rose immediately to control levels where it remained. The peak hyperemic response of that bed, barely noticeable at first, reached preocclusion levels within 3 hr. Circumflex peripheral pressure gradually dropped to 23 mm Hg in 3 hr and then stabilized at about 20 mm Hg, somewhat higher than the control of 14.

Eleven days after the release, the circumflex was again occluded abruptly. This time there were no changes in ECG, heart rate, or arterial blood pressure. The circumflex peripheral pressure rose steadily and rapidly; within 40 min it had reached 60 mm Hg.

The same trends were observed in dogs 6 and 7 (Table 1), which were also subjected to an initial abrupt circumflex occlusion. In dog 6 reocclusion was applied 5 days after release, and the circumflex peripheral pressure rose from 14 to 39 mm Hg within 1 hr, compared to an increase from 10 to 40 mm Hg following the initial occlusion of 3 days. Dog 7 had three reocclusions 30 days apart. The first and second reocclusion resulted in an increase in peripheral coronary pressure from 18 to 55 and 18 to 56 mm Hg, respectively, within 1 hr, compared to an elevation from 16 to 56 mm Hg after 2 days of the initial occlusion. The third reocclusion was performed under anesthesia and is treated below.

Retrograde flow from the circumflex was measured in dogs 5 and 7, after that artery had been opened for 5 and 30 days, respectively. In dog 5 the circumflex was occluded at the time of anesthesia and the retrograde flow, collected 1.5 hr later, was 40 ml/min. In dog 7 the circumflex was
reoccluded at the time of cannulation and repeated backflow measurements were made. Only a branch of the circumflex was cannulated. The collected flow of 3.2 ml/min at 1.5 min after occlusion rose rapidly and was 7.6 ml/min 30 min later.

Two normal dogs in the same weight range as in these experiments were selected at random and used for repeated backflow measurements following circumflex occlusion. The conditions were the same as for experimental dogs 4 and 7. The average heart rates of 140 and 150 were typical of anesthetized open-chest preparations; the blood pressures were 102 and 93 mm Hg. The backflow measurements were 2.7 and 3 ml/min at 1.5 min after occlusion, and 30 min later they were 2.8 and 3 ml/min—essentially the same.

The data for both groups show that following about 1 hr of reocclusion the collateral indices increased to levels attained only after days following the first occlusion. However, in dog 4 where the initial complete occlusion was maintained for only 1 day the increase in collateral indices was somewhat slower following reocclusion, and the ECG showed some slight, very transient, changes in the ST-T segment. In dog 3, peripheral circumflex pressure had reached 72 mm Hg 3 days after the first occlusion, but only 57 mm Hg or 21% lower after 1 hr of reocclusion.

Gross examination of the hearts revealed the following: the gradual occlusions resulted in minimal or no visible lesion. Dogs 1, 2, and 3 had normal myocardium including the interventricular septum and papillary muscles. Dog 4 had a small well-organized scar of about 1.5 mm in diameter in the posterior papillary muscle. The hearts from the dogs subjected to abrupt occlusion revealed massive infarcted areas, at times transmural, involving the lateral and posterior left ventricular walls.

**DISCUSSION**

This study was undertaken in order to detect the rapidity of regression of developed coronary collateral blood flow after removal of a circumflex occlusion, and its reappearance upon reocclusion. Although no method for the direct measurement of collateral flow through a coronary bed is known to us, the changes in the indices used here are believed to reflect the state of development and functioning of the collateral connections. Most of the blood supplying the circumflex bed after a complete occlusion must come from the other coronary arteries, particularly the left descending branch (6). An earlier report from this laboratory (8) supported this by the observation that as the left descending branch flow increases following gradual circumflex occlusion so does its peak hyperemic response. The present study shows (Fig. 3) that following circumflex occlusion a temporary closure (5 sec) of the descending branch causes the pressure in the circumflex to drop from 62 to 30 mm Hg. The residual pressure is probably contributed by the right coronary and septal arteries; many injected hearts from such preparations have shown large anastomotic connections from the right to the left coronary arteries (5, 8).

Immediately following circumflex occlusion in the present experiments, blood drawn distal to the point of closure was observed to be bright red and undoubtedly arterial. It has also been shown (1) that in the presence of well-developed collaterals such blood is arterial in composition. Furthermore, hearts injected after days of circumflex occlusion have revealed multiple large intercoronary connections exceeding 1 mm in lumen diameter at the surface of the heart (5, 8). We believe that following circumflex occlusion and significant collateral development peripheral coronary pressure is then largely a measure of circumflex bed perfusion pressure.

The same reasoning applies to the backflow measurements, but since backflow is collected against atmospheric pressure and without the importance of the bed normally supplied, it can only be regarded as an index of perfusion flow. In dogs 3, 4, 5, and 7, in which backflow was measured (open-chest conditions), reactive hyperemia of the circumflex bed was seen following each backflow collection, as evidenced by the increased arterial-coronary pressure gradient. This indicates that temporarily opening the circumflex to the outside for the backflow measurement deprived the bed of its blood supply (at least partially). And finally, a linear relationship has been shown between peripheral coronary pressure and backflow in the pressure range of 10 and 75 mm Hg (3).

Most importantly, following 3–12 days of partial occlusion in dogs 1, 2, 3, and 4, the circumflex branch had been maintained completely closed for 1–6 days. Still, gross examination of the hearts revealed no myocardial damage in dogs 1, 2, and 3 and only minimal scarring in the posterior papillary muscle of dog 4. The circumflex bed remained viable, while its normal blood supply was totally interrupted for up to 6 days, and must have been satisfied by the collateral circulation. Detailed microscopic examination in dog 3 and in dogs from other experiments in which the circumflex branch had been gradually occluded in a similar manner (8) confirms the absence of myocardial damage observed on gross examination.

On the basis of the indices used, it seems evident that shortly after release of an occlusion the rate of collateral blood flow regresses. This is further supported by the behavior of the peak hyperemic response to a temporary occlusion of both the descending and circumflex beds. Following the release after 3 days of original occlusion (Fig. 3), both the descending contribution to the circumflex bed during temporary circumflex occlusions (open circles and shaded area) and the descending peak hyperemic response decrease while circumflex hyperemic response increases. The circumflex bed thus appears to be relying less and less on the descending branch for its blood supply. Flow in the circumflex was usually re-established to control levels (Figs. 3 and 4). No hyperemic response was seen, indicating that at least during the resting conditions of these experiments the circumflex bed was satisfied by the collateral perfusion.

In all these experiments, when a reocclusion was applied the collateral indices rose steadily and rapidly. The left descending flow and the circumflex peripheral pressure rose within minutes to levels reached only after days following the first occlusion, without any apparent impairment of systemic and coronary dynamics or change in the ECG. This suggests that coronary collateral channels become nonfunctional when the need for them is removed,
but remain ready to resupply the affected myocardium within a very short time when a subsequent reocclusion occurs. The retrograde flow values obtained after 30 min to 1.5 hr of reocclusion are many times higher than those for normal dogs (4, 6). These reocclusions, performed up to 90 days following release of the original occlusion, always resulted in the collateral indices rising significantly within 1 hr or less, compared to the days required for comparable increases following the first occlusion.

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