Flow in the Major Branches of the Left Coronary Artery during Experimental Coronary Insufficiency in the Unanesthetized Dog

By Edward M. Khouri, Donald E. Gregg, and Howard S. Lowensohn

ABSTRACT

The dynamic changes in the coronary circulation and the response to drugs were studied following experimentally induced coronary insufficiency. Flow measurements were made in the left circumflex and descending branches of the coronary artery, and in the ascending aorta; pressures were measured in the ascending aorta and the left ventricle. As the left circumflex coronary artery branch was gradually constricted, reactive hyperemia following a 10-second occlusion of that vessel decreased. When the degree of constriction became such that the control resting flow began to fall, there was no reactive hyperemia, and the contractility index of the heart decreased. Within less than 24 hours, flow in the descending branch of the left coronary artery rose, and the cardiac contractility index returned to control; peak flow rate in the descending branch during reactive hyperemia after a 10-second occlusion also increased. The response to isoproterenol, nitroglycerin, and dipyridamole was similar in direction before and after the partial reduction of flow in the left circumflex coronary artery branch. The response was less in the coronary vessel with partial occlusion; in the unimpeded descending coronary artery branch, the response increased progressively. These results are consistent with the development of collateral vessels.

ADDITIONAL KEY WORDS

coronary occlusion collaterals vessel constrictor pneumatic cuff electromagnetic flowmeter

Previous studies of experimental coronary insufficiency and of the development of collateral circulation have been made following abrupt ligation of a coronary artery (1, 2), injection of foreign particles into the coronary circulation (3, 4), and gradual constriction of a coronary artery by an ameroid cuff (5, 6). The indices used to evaluate the degree of development of the myocardial collateral circulation include the radioisotope clearance technique, which gives an estimate of the collateral flow through capillaries (7), the change in flow into the unoccluded coronary arteries (8), and the retrograde flow and peripheral coronary pressure (1), which are, respectively, the blood flow and pressure beyond the site of occlusion. These measurements were made under open-chest conditions at various intervals after coronary insufficiency was induced, and control studies in the same animal were lacking. Elliot et al. (9), from this laboratory, made preliminary measurements of coronary blood flow, peripheral coronary pressure, and reactive hyperemia in the left circumflex branch of the conscious dog during partial and complete circumflex occlusion by an ameroid constrictor. However, the snug fit of the constrictor undoubtedly compromised the actual coronary flow and the ability of the circumflex bed to dilate (reactive hyperemia) during the first 10 days or so after operation while the dog was recovering. Actually, the control coronary flow values were quite unstable and decreased markedly during this period. The current availability of an adjustable coronary constrictor which can be controlled externally has
permitted an adequate (2- to 3-week) period of control observations before initiating coronary flow reduction. This has allowed establishment of a precise and meaningful relationship between coronary flow and reactive hyperemia.

The present report deals with the day-to-day changes in the systemic circulation and in the descending and circumflex branches of the left coronary artery following controlled constriction and occlusion of the circumflex branch of the left coronary artery in the unanesthetized dog.

Preparation and Methods

Healthy mongrel dogs weighing 22 to 28 kg were screened electrocardiographically to eliminate those with evidence of past myocardial ischemia. They were trained to lie at rest on a table for periods of 4 to 6 hours. When not being studied, the dogs were kept in large cages and were not subjected to exercise before or after surgery except for a short walk on the grounds two or three times a day.

Clean surgical technique was used, with autoclaving of all instruments and drapes. Under pentobarbital anesthesia and artificial respiration by a Harvard respirator pump with room air, a left thoracotomy was performed through the 5th intercostal space, and the various sensing and occlusive devices and catheters were installed (10). Electromagnetic flow transducers were placed around the circumflex and descending branches of the left coronary artery as close to their origin as possible, and around the ascending aorta. Pneumatic occlusive cuffs (12) were placed a few millimeters beyond the coronary flow transducers to obtain mechanical flow zeros. The adjustable hydraulic occlusive device was placed on the circumflex branch beyond the zero-flow cuff. Indwelling plastic catheters in the ascending aorta (13) and the left ventricle (in some dogs) were used to measure central aortic blood pressure and left ventricular pressure. The ventricular pressure tube was similar in construction to the aortic pressure catheter; the end in the ventricle was fitted with an olive-shaped piece of lucite. The opposite end, temporarily attached to a malleable silver probe, was introduced into the left ventricle via the left atrial appendage; the left ventricle was pierced with the probe from inside out at the apex and the tube drawn through it until the plastic "olive" rested against the inner wall of the apex. This catheter was placed in the coronary sinus. Because of unforeseen technical difficulties in analysis, the tube was not used to collect samples for metabolic studies but served as a convenient site for drug injection into the right atrium; because responses to drugs were delayed about 8 seconds, it is unlikely that there was any retrograde injection. The chest cavity was then closed in layers and the pneumothorax evacuated. Penicillin and streptomycin were administered...
intramuscularly before and for 7 days after operation. All catheters were flushed daily with saline and filled with a solution of heparin, 10 mg/ml.

The adjustable hydraulic occlusive device (Fig. 1) is made of one of our standard occlusive cuffs (12) constructed with a 50% thicker wall. The inflating end is essentially completely enclosed in a tight-fitting silver capsule so that expansion of the cuff impinges only on the vessel it surrounds. The external end is attached to a stainless steel micrometric piston. The whole system is filled with mercury.

Following recovery from surgery (7 to 10 days), with the dog lying on its right side, the blood flows in the circumflex and descending branches of the left coronary artery and in the aorta were determined daily during a control period of at least 4 to 6 days, and after partial and total occlusion of the left circumflex coronary branch. Similarly, a tangent to the cardiac output curve of blood in the aorta. Mean arterial blood pressure and mean flow rate in the ascending aorta were measured daily during a control period of at least 4 to 6 days, and after partial and total occlusion of the left circumflex coronary branch. The duration of the partial and total occlusion depended on how long the implanted devices functioned satisfactorily; the useful life of a preparation was 2 to 3 months. In addition, the circumflex and descending branches of the left coronary artery were occluded alternately for a period of 10 seconds, and the reactive hyperemia response of each bed was observed to determine its ability to dilate; both the peak flow rate, which occurs 2 to 5 seconds after release of the occlusion, and the response 15 seconds after the release were of special interest. Finally, isoproterenol, nitroglycerin, and dipyridamole were injected into the coronary sinus to determine the ability of the coronary vascular beds to dilate and the ability of the left myocardium to increase its external work in the presence of coronary insufficiency. The dose of each drug sufficient to give moderate systemic and coronary responses was established in preliminary experiments and was kept the same thereafter. Injection time was approximately 1 second. The response to these drugs was also observed following slow intravenous administration of propranolol to see if their effect was via beta adrenergic receptors. The dose of propranolol, 1 mg/kg, was sufficient to inhibit response to isoproterenol, 10 μg/kg.

The data were recorded continuously on an Electronics for Medicine DF-8 Recorder. Mean arterial blood pressure and mean flow rate in the left coronary artery branches and in the ascending aorta were determined by integration of the area under the phasic curves with a planimeter. The first derivative of the ventricular pressure during cardiac ejection yielded the acceleration of blood in the aorta. Short strips of record (not shown) taken at 300 mm/sec facilitated these estimations. The heart rate was calculated from the time interval between successive heart beats.

**Results**

Because these experiments required that many systems remain functional for a relatively long time, only three out of eight preparations were successful. The results reported here are based only on these three animals, in which the various implanted devices performed well for periods of 56, 59, and 81 days. Of the three, one was not fitted with a left ventricular pressure tube. Because of the exploratory nature of this work, the degree of occlusion was not made the same for all three animals. Generally, the rate and degree of constriction of the circumflex lumen were such that coronary insufficiency was evidenced but myocardial infarction was avoided. In two of the three dogs, the left circumflex branch was constricted slowly and gradually until reactive hyperemia disappeared and was maintained at this level for 3 to 5 days before the occlusion was completed. In the third dog, flow in the left circumflex branch was reduced abruptly to about 25% of normal and held at this level for 7 days before completion of the occlusion.

The criteria used to indicate the degree of coronary insufficiency were the level of flow in the partially occluded circumflex vessel and the extent of dilatability in its vascular bed. No change in ST-T segment of the electrocardiogram. Changes in the QRS complex and ventricular arrhythmias were avoided. The criteria used to estimate compensation were the rise in flow and the level of reactive hyperemia in the descending branch of the left coronary artery and the extent of the systemic and coronary responses to the three drugs. The responses to coronary insufficiency and to the various tests were not always quantitatively the same, and no attempt is made to compare...
Control and peak flow rate during reactive hyperemic response following a 10-second occlusion of the circumflex branch of the left coronary artery before and after partial occlusion of that vessel. HR = heart rate. ECG = lead II of the electrocardiogram. LDCF and LCCF = left descending and left circumflex flow, respectively (numbers indicate mean flow in ml/min). CABP = central aortic blood pressure (numbers indicate mean pressure in mm Hg). LVP = left ventricular pressure. LVEDP = left ventricular end-diastolic pressure (numbers indicate pressure in mm Hg). CO = cardiac output minus coronary blood flow (numbers indicate cardiac output in liters/minute). Four to eight consecutive cardiac cycles were used to obtain the mean flow and pressure values; the actual number used depended upon the degree of the sinus arrhythmia. Horizontal lines to the right of the symbols for coronary flows and aortic blood pressure represent zero coronary flow and zero pressure. \( \frac{dP}{dt} \) = rate of rise of left ventricular pressure. Vertical lines are 0.2 seconds.

Figure 2 illustrates the findings as circumflex constriction was adjusted to prevent reactive hyperemia without essentially altering circumflex flow. The sinus arrhythmia, low heart rate, and low flows in the left coronary branches (control panel A) before circumflex constrictions.

one dog with the others in this study. The direction of the response, however, was always similar, and the results presented are regarded as typical. Some additional supporting evidence was obtained from two preliminary experiments (not included above) in which the flow in the descending branch of the left coronary artery and the left ventricular pressure were not measured. The dogs experienced no pain or discomfort, as evidenced by a lack of apprehension, restlessness, or whining.

Figure 2 illustrates the findings as circumflex constriction was adjusted to prevent reactive hyperemia without essentially altering circumflex flow. The sinus arrhythmia, low heart rate, and low flows in the left coronary branches (control panel A) before circumflex constrictions.
Adjustments in the systemic and left coronary circulation following an abrupt reduction to 25% of resting flow in the left circumflex coronary branch, and the response to intracoronary injection of isoproterenol and nitroglycerin. Record of response to nitroglycerin was taken at 7 to 9 seconds after drug injection at time of maximum coronary response to the drug. Gain of amplifiers for variables measured was kept constant throughout. $dV/dt^*$ = acceleration of blood in the aorta. Otherwise symbols and time lines as in Figure 2.

constriction are characteristic of a good operative recovery in a resting animal. Following release of a 10-second occlusion (panel B), the left circumflex coronary flow rose to 75 ml/min, approximately three times the control of 24 ml/min. This ratio of peak reactive hyperemia flow rate to control flow rate varied from 3 to 6 in the dogs in this study. Initial partial constriction of the circumflex branch (not shown) did not affect the coronary flow rate but reduced the amplitude of the flow pattern and decreased greatly the peak reactive hyperemia (panel C). This decrease in reactive hyperemia was the first dynamic change observed when a gradual occlusion was slowly applied to a coronary artery. In-
The left column shows the control flow rate before occlusion (top panel), after 4 days of partial occlusion (center panel), and after 7 days of partial plus 14 days of total occlusion (bottom panel). The center and right columns show the flow rate during peak reactive hyperemia response to a 10-second occlusion, and the flow rate 15 seconds after the release, before and after partial and total occlusion of the left circumflex coronary artery branch. Gain of amplifiers for the measured variables was kept constant throughout. During the recording of the last row (7 days partial + 14 days total occlusion), the magnet current for the aortic flow transducer was inadvertently set too low, and no absolute values for the cardiac output can be shown. However, no relative changes are seen between the three panels of that row. Symbols and time lines as in Figure 2.

Increased partial constriction 24 hours later (not shown) further decreased the flow and now slightly reduced circumflex flow and essentially prevented the reactive hyperemia (panel D). The rise in descending flow to 29 ml/min from 23 ml/min (panel A) is suggestive evidence of rapid development of collateral vessels in the presence of an essentially normal resting circumflex flow. Except for a mild increase in heart rate and decrease in dP/dt (panel D), the dynamics of the systemic circulation did not change.

Figure 3 (upper row), taken from a second dog, shows the compensation that takes place with time in the systemic and left coronary circulation after the resting circumflex...
flow was reduced in one step by about 75% from 57 to 14 ml/min. Within the first hour, the dynamics of the systemic circulation, except for the heart rate, decreased mildly while left descending flow increased by 34% to 43 ml/min. Subsequent daily observations showed systemic dynamics to have returned to normal within a day or so. Left descending flow rose progressively to 60 ml/min by the seventh day. On the seventh day, total occlusion (record not shown) did not affect cardiac dynamics but the left descending flow continued to increase to 70 ml/min. Thus there occurred an increase of 100% in the descending flow and a restoration to 80% of the resting preocclusion flow in the two coronary branches.

Figure 3 (lower two rows) shows the response to the injection of isoproterenol, 1 μg iv, and nitroglycerin, 0.3 mg iv. Before constriction, isoproterenol considerably increased flow in both the descending and circumflex branches, cardiac output, cardiac work, and $d^2V/dt^2$. After 1 hour of reduction of circumflex flow, the increase in cardiac output, cardiac work, and $d^2V/dt^2$ was only moderate, while 7 days later it was of the same magnitude as before constriction. The response to nitroglycerin at 7 to 9 seconds after injection was a large coronary dilation, a moderate decrease in blood pressure, and very little change in the other parameters. Following constriction of the circumflex branch, as the descending flow increased with time, the same dose of nitroglycerin caused a larger flow in that vessel. The response to 5 mg of dipyridamole was similar to the early response to nitroglycerin (record not shown).

Figure 4 illustrates the reactive hyperemia response at its peak and at 15 seconds in the descending branch before and after partial and total occlusion of the circumflex branch. As in Figure 3, such constriction caused the descending flow to almost double. Before occlusion (top row), the reactive hyperemia responses (179 ml and 88 ml) at the two selected periods were 5 times and 2 times the control flows, respectively. After 4 days of partial occlusion (descending flow reduced to 14 ml/min) and after 7 days of partial plus 14 days of total occlusion, the reactive hyperemia responses of 195 ml and 74 ml, 222 ml and 88 ml, were greater than those in the control panel. However, the

Figure 5

The left coronary and systemic responses to intracoronary sinus injection of isoproterenol, nitroglycerin (TNG), and dipyridamole, before and after propranolol, prior to coronary occlusion. Symbols and time lines as in Figure 2.

Coronary Research, Vol. XXIII, July 1968
ratios of the early and late reactive hyperemia responses to their control flow rates decreased mildly as compared to the ratios before artery constriction.

Figure 5 shows the response to isoproterenol, nitroglycerin, and dipyridamole before and after administration of propranolol, 1 mg/kg iv, prior to coronary occlusion. As would be expected, propranolol blocked the response to isoproterenol. Typically, nitroglycerin caused first a large coronary dilation, followed by a systemic effect manifested by a drop in blood pressure and a marked increase in heart rate, acceleration of blood in the aorta, and cardiac output. Segments of record are shown during both maximum coronary response (max. cor. resp.) which occurs 7 to 9 seconds after injection, and maximum systemic response (max. syst. resp.) as evidenced by the peak increase in cardiac rate and contractility index which is seen about 10 seconds later. During the second phase of the response, the coronary flow was only moderately elevated above the control level. Following beta-receptor blockade, the early response to nitroglycerin during maximum coronary response was the same as before. During maximum systemic response, the acceleration of blood in the aorta did not rise as much, increasing from 12 to 14 liters/sec² as compared to a rise from 12 to 17 liters/sec² before propranolol. The response to dipyridamole was the same as before beta-receptor blockade; the blood pressure was somewhat better maintained.

Figure 6 shows the response to the same drugs before and after administration of propranolol in the presence of a total obstruction of flow in the circumflex branch of the left coronary artery. Total occlusion was induced after 7 days of partial occlusion; results shown were obtained within 3 hours of the complete closure. Following propranolol, the coronary and systemic systems were not altered, and there was no response to isoproterenol. The main difference in the responses to nitroglycerin and dipyridamole was that following beta-receptor blockade, the systemic effect of the drugs was minimized; the cardiac contractility index did not rise as much, and there was a smaller drop in blood pressure. As a consequence, the increase in coronary flow rate in response to nitroglycerin, although not as large initially, was more...
EXPERIMENTAL CORONARY INSUFFICIENCY

sustained, and the coronary response to
dipyridamole was larger.

Electrocardiograms obtained during the
course of these experiments showed tran-
sient ischemia as evidenced by fluctuating
ST-T segment changes but no QRS changes.
At the end of the experiments, cineangiog-
raphs were taken. In the three dogs, exten-
sive collateral development from the left
descending branch could be seen and the
left circumflex branch filled well retrogradely
to a point just short of the occluding cuff. The
animals were then killed. The heart of one
of the two dogs in which occlusion was in-
duced slowly and gradually, was injected by
the Schlesinger technique (14) and compared
to the heart of a normal dog similarly in-
jected. In the heart of this animal, killed 41
days after the initial constriction, there was
extensive filling of the left circumflex area.
The diameter of the intercoronary connections
measured 350 to 1200 μ. In the normal dog,
the bed supplied by the descending branch
was well delineated, with no connections to
the left circumflex branch. Cross examination
of the second heart (gradual occlusion of the
artery) revealed normal myocardium includ-
ing the interventricular septum and papillary
muscles; no focal lesions were present. Ex-
amination of the third heart (abrupt occlu-
sion) revealed only a very small, well-or-
organized scar in the posterior papillary muscle.
Microscopic examination showed that the
subendocardial third of the posterior papil-
lary muscle had several regions of extensive
fibroblastic proliferation and necrotic muscle
fibers. Acute inflammatory changes had also
occurred in these regions as evidenced by the
presence of polymorphonuclear and mono-
nuclear cellular infiltrates.

Discussion

During these studies, it was assumed that
the occlusive device did not change signifi-
cantly once it was set for a given degree
of constriction. This assumption, although not
essential to the conduct of the experiments,
makes the observed changes in the coronary beds
directly related to the compensations
taking place. In the experimental studies when
the degree of constriction was made severe
enough to override the ability of the heart
to compensate, as seen in Figures 3 and 4,
the flow in the partially occluded bed re-
mained constant at 14 ml/min. Tests con-
ducted in vitro, in constant temperature baths,
support this assumption.

Before constriction and occlusion of a coro-
nary artery, it was important to establish a
reliable test to determine the extent and
constancy of the ability of the normal coronary
vascular bed to dilate under controlled resting
conditions. Another attempt (9) from this
laboratory was unsuccessful because it was
not possible to obtain reliable control values
in the presence of an ameroid constrictor.
The observations reported here using a con-
trollable constrictive device permitting a long
control period indicate that the peak flow
response during reactive hyperemia is four to
six times the control flow. In these and other
experiments (15), longer periods of occlusion
did not increase this peak flow rate but rather
the duration of the response. As many as 13
occlusions of 10-second duration on the same
day, for periods of up to one week, did not
affect the reactive hyperemia response; com-
plete recovery (15 to 20 minutes) had been
reached between the occlusions. Under the
influence of mild dosages of coronary vasodi-
lators or myocardial stimulant drugs, this ratio
of peak response to control was smaller,
principally because the control flow had in-
creased; however, the flow rate during peak
response did not change significantly. Finally,
in other unpublished experiments, the maxi-
mum coronary flow response to heavy exer-
cise, excitement, and to larger doses of the
drugs, was no greater than in reactive
hyperemia. These observations indicate that
a 10-second occlusion of a coronary artery
maximally dilates its bed and that the peak
reactive hyperemia response is indicative of
the ability of a coronary bed to adjust and
compensate for a stress such as coronary
constriction or occlusion. Therefore, monitor-
ing the decrease in reactive hyperemia during
development of experimental coronary insufficiency should serve as a sensitive indicator of the compensatory ability of the coronary bed. The finding here that the normal resting coronary flow is approximately maintained until reactive hyperemia approximates zero is an important application of this tool.

Most of the blood now supplying the microcirculation of the insufficient left circumflex coronary bed must, of course, come from the other nonoccluded coronary arteries. The compensatory changes observed in the left descending branch indicate a very large reserve. Even when the resting flow in the circumflex branch was abruptly reduced to about 25% of normal, the flow in the descending branch rose within a few hours; the level of reactive hyperemia in the descending bed and its ability to respond to vasodilators and the ability of its myocardium to meet the demands of increased cardiac work were, after temporary and moderate reduction, restored to normal within a day or so. It is believed that the large increase in flow in the descending branch represents mainly perfusion of a larger mass of myocardium, because of the demonstration by injection and cineangiography of sizeable communications between the left circumflex and descending branches and the right coronary artery. However, some of the increase could be the result of the left descending portion of the myocardium having to contribute more work to maintain proper cardiac function.

It has been reported that myocardial infarction following a coronary artery occlusion in open-chest dogs is possibly a reflex mechanism and that adrenergic neurone blockade prevents such infarction (16). Using an external cuff rather than internal emboli, we have not observed signs of coronary reflex activity. Beta-receptor blockade, early and late after induction of coronary insufficiency, has failed to elicit significant flow changes in either the descending or the circumflex branch of the left coronary artery. Dissection of the coronary artery for implantation of the flow transducers and occlusive devices undoubtedly causes injury to some nerves. There is, however, considerable evidence to support the view that the autonomic control of the heart is still functional. Histological study of the pericoronary nerve supply has failed to demonstrate significant neural damage (17). In addition, following such operative procedures, the coronary circulation responds almost instantaneously and without apparent physiological impairment to stresses such as exercise and excitement (13, 18) and to electrical stimulation of the left stellate ganglion previously severed from the spinal nerves and sympathetic chain (19). The possibility still remains, however, that reflex vasoconstriction could occur at the level of small vessels causing a redistribution of coronary flow without affecting flow in the large vessels. Nevertheless, it would seem unlikely that an unequal distribution of flow had serious consequences in these experiments since ventricular fibrillation did not occur and myocardial infarction was essentially absent.

Acknowledgments

We are indebted to Dr. Colin M. Bloor for the pathology studies, and to Dr. Arthur S. Leon for the interpretation of the electrocardiograms.

References

Flow in the Major Branches of the Left Coronary Artery during Experimental Coronary Insufficiency in the Unanesthetized Dog
EDWARD M. KHOURI, DONALD E. GREGG and HOWARD S. LOWENSOHN

Circ Res. 1968;23:99-109
doi: 10.1161/01.RES.23.1.99

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1968 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

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

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

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