Coronary Inflow and Outflow Responses to Coronary Artery Occlusion

By Thomas E. Driscoll, M.D., and Richard W. Eckstein, M.D.

ABSTRACT
Sudden complete occlusion of a major coronary artery (left circumflex or right coronary artery) was produced in anesthetized dogs. The effect on arterial inflow, venous outflow and O₂ saturation of coronary venous blood from the nonischemic left ventricle was studied. The usual response to occlusion of the left circumflex artery was an increase in flow in the left anterior descending artery and in outflow from the great cardiac vein. The O₂ saturation of venous blood from the nonischemic muscle decreased. These changes did not occur following occlusion of the right coronary artery. It was not possible to measure tissue pressure accurately to relate this measurement to flow changes. Observations on coronary sinus flow and O₂ saturation were also made following occlusion of the left circumflex artery and retrograde flow collection from it. These observations plus the changes in anterior descending inflow and great cardiac vein outflow with coronary occlusion suggest that these changes are more likely due to alterations in O₂ consumption of the nonischemic muscle rather than to changes in flow through interarterial or non-interarterial collateral vessels.

ADDITIONAL KEY WORDS coronary reflex myocardial pressure venous oxygen cardiac metabolism collateral circulation anesthetized dogs

Several investigators have reported that occlusion of a major branch of a coronary artery results in an increased flow in adjacent coronary arteries (1-6). The mechanism of this response is not known. Reflex vasodilation is one possibility; a second is that collateral flow increases into surrounding muscle; a third is that vasodilatation occurs secondary to an increased O₂ requirement by the nonischemic muscle. Recently, Herzberg et al. presented evidence that a fall in extravascular pressure in the nonischemic zone occurs and allows a passive increase in arterial inflow (6). It is also conceivable that vasodilator metabolites from a partially ischemic border zone could diffuse into or otherwise reach the nonischemic muscle and thereby cause the increase in inflow. In an attempt to clarify the physiological basis for this inflow response to coronary artery occlusion, the following experiments were done.

Methods and Results
Dogs weighing 15.0 to 24.5 kg were anesthetized with morphine sulphate (98 mg) subcutaneously followed in 30 min by pentobarbital (20 mg/kg) intravenously. Additional pentobarbital was given intravenously as needed during the experiments. During positive pressure respiration, the fourth or fifth intercostal space was entered, the pericardium was opened, and the appropriate coronary vessels were isolated and cannulated. At times the coronary arteries were perfused at constant pressure from a reservoir which received blood from the animal via a Sigmamotor pump. Heparin (300 mg) was given intravenously to prevent clotting. An adjustable clamp was placed around the descending thoracic aorta to regulate arterial pressure above it. Arterial pressure was measured from a carotid artery by a Statham P23Cb pressure transducer and was recorded on an Electronics for Medicine DR-8 recorder. In some experiments left ventricular pressure was recorded using a Statham transducer connected to a metal cannula inserted into the left ventricle through the cardiac apex. Our studies were arranged in several groups.
In this group of animals, the left anterior descending artery was cannulated at its origin and perfused from a constant pressure reservoir or from the aorta via a cannula inserted through the left subclavian artery. Coronary inflow was metered by a Shipley-Wilson rotameter or a pulsed field electromagnetic flowmeter (Statham Instrument Co.). The flowmeter probe was a cannulating, or flow-through type, and was interposed in the flow circuit between the constant pressure reservoir and the perfused coronary artery. The zero level for coronary inflow was determined immediately after each experimental observation by diverting the entire flow around the meter via a by-pass circuit. Calibration of the meter was done at the end of each experiment by perfusing the animal's blood through the meter at known flow rates. Zero flow level during calibration was obtained by clamping the rubber tubing of the flow circuit in the same location as was done during the experiment. This was necessary to avoid baseline shifts which frequently occurred when the tubing was clamped at different locations between the flowmeter and an external ground connection.

The left circumflex artery was either cannulated at its origin or encircled by a polyethylene snare. In 7 experiments a similar loop was also placed around the origin of the right coronary artery. In order to relate venous outflow rate and O2 content to the left anterior descending arterial inflow, the great cardiac vein was isolated and cannulated. This vein, which drains a fraction of the venous outflow from muscle supplied by the left anterior descending artery, was cannulated at the level of the origin of this artery by a metal tube (1.2 mm long; i.d., 1.0 to 1.5 mm) to which was attached polyethylene tubing (PE 200-260) and a segment of rubber tubing. The great cardiac vein flow was returned to the animal's left jugular vein or right atrium; the vein was allowed to bleed freely during cannulation so that it was not obstructed at any time. Venous blood from the muscle supplied by the left circumflex artery (and that fraction of muscle supplied by the left anterior descending artery not draining into the great cardiac vein) was collected by cannulation of the coronary sinus as will be shown.

Oxygen saturation of blood in the great cardiac vein was monitored by drawing 6 to 8 ml/min of it through a cuvette densitometer (Gilford Instrument Co.). A spacer 0.68-mm thick was used in the cuvette to accommodate the low flow rates from the vein. From a sheet of brass 0.46-mm thick, a disc was cut to fit the cuvette. A vertical slit 1-mm wide was made along the diameter of the disc to allow light to reach the photocell. Teflon gaskets 0.11-mm thick with an identical 1-mm wide slit were placed on each side of the brass spacer. A cylindrical lens machined from a lucite rod was placed between the light source and cuvette to focus a narrow vertical beam on the slit. By these modifications instrument sensitivity was preserved at low venous flow rates. The densitometer was calibrated from measurements of oxygen saturation (7) and hemoglobin concentration made on the great cardiac vein blood samples. To obtain venous samples at various levels of O2 saturation, left anterior descending artery perfusion pressure was temporarily varied. Great cardiac vein flow was measured by timed collections in a graduated cylinder or by a cannulating type electromagnetic flowmeter (Biotronex) placed in the outflow circuit distal to the site of sampling through the densitometer. The flow through the densitometer was added to the measured outflow to obtain total great cardiac vein outflow. Calibration and zero flow levels were determined as for coronary arterial flow.

After control measurements of arterial pressure, left anterior descending arterial inflow, and great cardiac vein outflow and O2 saturation, the left circumflex or right coronary artery was occluded for 60 sec. In all experimental observations it was necessary to increase aortic resistance with the aortic clamp during circumflex artery occlusion to maintain mean aortic resistance constant above the clamp. (The significance of this is discussed later.) The coronary artery was then opened and measurements made during re-
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Effect of occlusion of the circumflex artery on flow in the left anterior descending artery and oxygen saturation in great cardiac vein. AP = mean aortic pressure (electronically damped), G.C.V. O₂ sat. = great cardiac vein O₂ saturation, and L.A.D. Flow = flow in left anterior descending artery.

Effect of circumflex artery occlusion on flow and O₂ saturation in great cardiac vein. G.C.V. Flow = flow through great cardiac vein. Remainder of legend as in Figure 1. Aortic pressure electronically damped.

dovery. During each experiment, hemoglobin concentrations were held constant by varying the rate of an intravenous infusion of 0.2% NaHCO₃ and 5% dextrose in water; 250 to 500 ml were required. Hemoglobin concentration was determined on each blood sample at intervals during the experiments; it varied less than 0.3 g/100 ml on samples drawn before and after arterial occlusion.

Occlusion of the left circumflex artery was produced 97 times in 20 experiments; flow in the left anterior descending artery increased 87 times. In 84 observations, the increase in flow averaged 11.01 ± 3.92 ml/min. The flow increase was gradual, reached a plateau in about 30 sec, and remained elevated for 20 to 30 sec after release of the occlusion (Fig. 1). Thereafter, flow returned slowly to control value. In 25 experiments, great cardiac vein O₂ saturation was measured during occlusion of the left circumflex artery; it decreased 80 times in 82 observations (Fig. 1). In 14 ex-
experiments in which O$_2$ content was measured, it decreased by 0.5 to 4.1 (mean $= 1.80 \pm 0.88$) ml/100 ml blood.

In 16 experiments outflow from the great cardiac vein was measured and ranged from 15 to 35 ml/min at mean aortic and coronary perfusion pressure of 100 mm Hg. During occlusion of the left circumflex artery, great cardiac vein flow increased 52 times in 66 observations (mean increase $= 3.27 \pm 2.68$ ml/min). No significant change occurred in the remaining 14 observations. The response to the circumflex artery occlusion is illustrated in Figure 2 along with the simultaneous decrease in great cardiac vein O$_2$ saturation. After release of occlusion, venous flow temporarily increased further before returning to control and O$_2$ saturation rose above its starting value.

Right coronary artery occlusion was produced 14 times in 5 experiments. On no occasion was there a change in left anterior descending artery flow, or great cardiac vein flow and O$_2$ saturation. For example, in 1 experiment, right coronary artery occlusion was maintained for 60 sec; left anterior descending arterial flows before and during occlusion were 31.0 ml/min and 31.5 ml/min respectively; great cardiac vein flows were 13.2 ml and 13.5 ml/min and the O$_2$ saturations were 17% and 16.5%.

Phasic left anterior descending arterial flow was recorded (Biotronex electromagnetic flowmeter) 25 times in 6 experiments. End-diastolic flow rate increased in 23 observations (mean $= 8.58 \pm 5.66$ ml/min), decreased slightly once, and showed no change on one occasion during occlusion of the left circumflex artery. Left ventricular diastolic pressure also increased during occlusion and returned to its starting value after release. Phasic flow and left ventricular pressure changes from 1 experiment are shown in Figure 3.

**Part II**

Coronary artery occlusion was produced under several different circumstances. The experimental preparation was the same as in Part I except for the following modifications. Polyethylene snare loops were placed around the superior and inferior vena cava at their entrance into the right atrium. Great cardiac vein flow was diverted to the right atrium. The left anterior descending and left circumflex arteries were cannulated and received oxygenated blood at constant pressure from a reservoir. The superior and inferior vena cava

![Figure 3](http://circres.ahajournals.org/)

**FIGURE 3**

Effect of circumflex artery (circ.) occlusion on end-diastolic flow in the left anterior descending artery (L.A.D.). HR = heart rate, AP = aortic pressure, LVP = left ventricular pressure. The electromagnetic flowmeter was damped and rapid flow changes during systole and early diastole are not accurate.

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were then occluded and the thoracic aorta clamp was released (2 experiments). After aortic pressure, left anterior descending arterial inflow and great cardiac vein outflow had stabilized (1 to 2 min after caval occlusions), occlusion of the left circumflex artery was produced and maintained for 30 sec. (The flows and great cardiac vein O₂ saturation or just the O₂ saturation was monitored before, during, and after release of occlusion.) Circumflex arterial occlusion was then released and following recovery of the left anterior descend-

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**FIGURE 4**

Effect of left anterior descending artery (L.A.D.) occlusion on coronary sinus (C.S.) flow. AP = mean aortic pressure (electronically damped).

**FIGURE 5**

Effect of circumflex occlusion and subsequent collection of circumflex retrograde flow on coronary sinus oxygen saturation (C.S. O₂ sat.) and coronary sinus flow (C.S. flow). AP = mean aortic pressure (electronically damped). Note constant C.S. flow between occlusion of the circumflex and start of back bleeding through the circumflex artery. The latter resulted in a rise in C.S. O₂ saturation and decrease in C.S. flow. When the circumflex artery was reperfused there was reactive hyperemia (not shown) in the bed supplied by the left circumflex artery and C.S. flow increased above control levels. C.S. O₂ saturation temporarily decreased as blood which has been in the ischemic muscle supplied by the circumflex artery was perfused into the C.S. The subsequent marked increase in O₂ saturation is due to reactive hyperemia in the bed supplied by the left circumflex artery.
ing artery and great cardiac vein flows, caval occlusions were released. During measurements, the left ventricle ejected only the bronchial and coronary venous return. Ventilation was unchanged during caval occlusions so that the ventilation to perfusion ratio in the lungs increased greatly. No measurements were made of pulmonary venous Po₂ or Pco₂; however, both arteries were perfused with blood from the reservoir before, during, and after the caval occlusions and no blood from the animal entered the reservoir during and immediately after caval occlusions.

In 2 additional experiments, ventricular fibrillation was produced by a 60-cycle current applied to the ventricular muscle. The left anterior descending and left circumflex arteries were perfused by oxygenated blood from a reservoir at constant pressure (40 to 60 mm Hg during fibrillation). When aortic pressure, left anterior descending arterial flow and great cardiac vein flow were steady, left circumflex artery occlusion was produced for 30 sec and then released. Measurement of the flows and great cardiac vein O₂ saturation were made as in the caval occlusion experiments.

In 2 further experiments in which the design was as in Part I, 5 to 10 mg of dipyridamole¹ was injected into the cannulated left anterior descending and left circumflex arteries. If there was no reactive hyperemia after a 10-sec occlusion, the vascular beds were considered to be maximally dilated. When maximum dilation was achieved, the left circumflex artery was occluded for 30 to 60 sec and then released. The two flows and great cardiac vein O₂ saturation were measured as described in the caval occlusion experiments.

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¹Persantin was purchased from Geigy.
from the left circumflex artery was collected for 20 to 60 sec after occluding it, coronary sinus flow further decreased and coronary sinus O\textsubscript{2} saturation increased as interarterial flow from the left anterior descending to the left circumflex artery was prevented from entering the ischemic muscle supplied by the circumflex artery (Fig. 5). When retrograde flow from the circumflex artery was collected, the initial fall in coronary sinus O\textsubscript{2} saturation was similar in magnitude to the average decrease in great cardiac vein O\textsubscript{2} saturation following occlusion of the left circumflex artery with or without back bleeding. One example of this is shown in Figure 6. The initial decrease in coronary sinus O\textsubscript{2} saturation is 5.8% during circumflex back bleeding. As occlusion was maintained, but interarterial flow was allowed to perfuse the muscle supplied by the circumflex artery (back bleeding stopped), O\textsubscript{2} saturation decreased further by 11%. The significance of this is discussed below.

Numerous attempts were made to measure myocardial tissue pressure by modifications of several different techniques (8-10). However, in the presence of coronary artery occlusion, considerable errors and artifacts occurred and the results were considered unsatisfactory.

**Discussion**

The consistent findings in these experiments are: During coronary artery occlusion, flow into the nonischemic muscle supplied by the left anterior descending artery increased, venous flow (great cardiac vein) from the nonischemic muscle increased and its venous O\textsubscript{2} saturation decreased (Figs. 1 and 2). Although it has been suggested that reflex coronary constriction results from occlusion of adjacent coronary arteries (14), the increase in arterial inflow in the nonoccluded artery in the present experiments is in agreement with the studies reported by most other investigators who found that coronary resistance predominantly decreases in adjacent, nonoccluded vessel (1-6). The observed decrease in O\textsubscript{2} content and increase in flow in the great cardiac vein do not support the concept of reflex dilatation of the left anterior descending artery which it drains. Following coronary artery embolization however, a vasoconstrictor response was observed by Guzman (11) in non-embolized arteries; this was largely blocked...
by atropine. The constrictor response seen by Mosches et al. (13) and the dilator response found by West et al. (12) were not affected by a variety of drugs and surgical procedures designed to eliminate possible coronary reflexes.

Occlusion of the left circumflex artery caused an increase in end-diastolic and mean flow rate in the left anterior descending artery even when heart rate did not change (Fig. 3). The rise in mean flow is therefore not due solely to a change in mechanical compression of vessels during systole or to a decrease in the systole-cycle ratio brought about by circumflex occlusion. The rise in end-diastolic flow reflects a true decrease in vascular resistance since perfusing pressure (aortic or reservoir pressure) was held constant. This fall in resistance could result from active vasodilation of vessels supplying nonischemic muscle, of collateral vessels into ischemic muscle, or from a passive stretching of resistance vessels due to a decrease in extravascular support.

In the present experiments, attempts to measure accurately myocardial tissue pressure following coronary artery occlusion were unsuccessful. Therefore, we could not confirm the finding of Herzberg et al. (6) who observed a decrease in extravascular myocardial tissue pressure in nonischemic, as well as the ischemic zones following coronary artery occlusion. Even if myocardial tissue pressure does fall in the nonischemic muscle, experiments reported here indicate some other mechanism is primarily responsible for the inflow rise in the nonischemic muscle since the directional change in venous O₂ saturation observed was contrary to that expected from a fall in tissue pressure alone. A passive decrease in extravascular pressure allowing an increase in arterial flow would result in over perfusion and the venous O₂ saturation would rise. In the experiments described here, great cardiac vein O₂ saturation always decreased. In addition, no evidence of an autoregulatory flow pattern in the arterial flow curve was seen as occurs when cardiac muscle is over perfused by raising perfusion pressure (15).

Some authors (3, 4) have suggested that the rise in coronary inflow under these experimental conditions may be partly due to a functional overlap of collateral vessels between adjacent coronary arteries and that flow through these collateral vessels is exaggerated by the pressure gradient between the non-occluded and occludal arteries. By this mechanism the increase in left anterior descending arterial flow after left circumflex artery occlusion would be distributed to the muscle supplied by the circumflex artery through interarterial or other collateral vessels or to a border zone between the two arteries or both. Several arguments can be stated against these possibilities.

Interarterial flow into the muscle supplied by the circumflex artery of sufficient magnitude to explain the rise in left anterior descending arterial inflow is unlikely in the present experiments for five reasons: (1) The flow in the great cardiac vein increased (the increase in this flow is less than the left anterior descending arterial flow rise because the great cardiac vein drains only a fraction of the muscle supplied by the left anterior descending artery), (2) the increase was not prevented by allowing the circumflex artery to bleed backwards to the atmosphere to remove interarterial flow. If a significant fraction of the left anterior descending arterial flow rise was due to flow through interarterial collaterals into the muscle supplied by the circumflex artery and from there into the great cardiac vein, removal of interarterial flow by allowing the circumflex artery to bleed backwards should have reduced the venous flow, (3) coronary sinus flow remained constant after the initial fall caused by circumflex arterial occlusion (left anterior descending arterial flow was increasing and if interarterial flow into muscle supplied by the circumflex artery were increasing significantly, coronary sinus flow would rise during the period of occlusion), (4) the lack of an immediate decline in left anterior descending arterial flow following circumflex artery release (Fig. 1) is strong evidence against a substantial connection (interarterial) between the two arteries, and (5) in normal dogs interarterial flow is small and is increased by only small amounts even when...
large interarterial pressure gradients are created (15).

The question as to whether there is a rise in non-interarterial flow into the ischemic circumflex area or into a border zone as suggested by Levy (16) or both is more difficult to answer. However, the evidence from our experiments suggests that significant non-interarterial flow into the ischemic circumflex area is unlikely. This conclusion is based primarily upon the fact that distal coronary sinus flow during retrograde circumflex arterial bleeding does not rise during the time period when left anterior descending arterial flow is increasing (Figs. 5 and 6). A progressive augmentation of the volume of venous drainage would have been expected had non-interarterial flow into the area increased. Also, Figure 6 shows the distal coronary sinus O2 content decreased to 5.6 ml/100 ml blood when retrograde bleeding of the circumflex artery was stopped. This occurs even though blood flow through the ischemic tissue is increased as is evidenced by an elevation of distal coronary sinus flow from 9 to 17 ml/min. We believe that had a significant volume of non-interarterial flow entered the ischemic muscle during retrograde bleeding of the circumflex artery, the O2 content of the distal coronary sinus would have been decreased to a level similar to that measured when the muscle was perfused by blood from interarterial channels (i.e., during circumflex occlusion without back bleeding). Actually, the degree of fall in the O2 content of the distal coronary sinus during retrograde bleeding from the circumflex artery is of the same magnitude as that which occurs in the great cardiac vein during occlusion of the left circumflex artery (Figs. 1 and 2). This suggests that the blood in the distal coronary sinus during retrograde bleeding from the circumflex artery chiefly enters there by way of communications with the great cardiac vein and is drainage from the muscle supplied by the anterior descending artery. This is supported because occlusion of the left anterior descending artery results in an immediate considerable decline in distal coronary sinus flow (Fig. 4) while, in contrast, occlusion of the circumflex artery results in no decline in great cardiac artery flow (Fig. 2).

Another possible cause for the decrease in great cardiac vein O2 saturation during left circumflex occlusion is that a change in contraction of the nonischemic muscle occurs. The ischemic area of muscle has been shown to bulge during systole rather than contract. This begins 6 to 9 sec after coronary artery occlusion (17). Since in the present experiments aortic pressure was maintained constant, the nonischemic muscle may have contributed more tension to maintain ventricular and aortic pressure in compensation for the loss of function of the ischemic muscle. Left ventricular end-diastolic pressure increased during occlusion of the circumflex artery and even if left ventricular volume (radius) did not change, the cardiac muscle fibers would be under a greater initial tension, since tension = pressure × radius. Under this circumstance, an increased myocardial O2 consumption would be expected. A rise in myocardial O2 consumption in the nonischemic zone would explain the observed rise in great cardiac vein flow and fall in its O2 saturation. The absence of changes in the left anterior descending arterial flow and great cardiac vein flow and its O2 saturation after right coronary occlusion is another reason for relating the changes which occurred during left circumflex occlusion to left ventricular work (metabolism). When the factor of external cardiac work was eliminated (empty beating hearts or fibrillating hearts), occlusion of the left circumflex artery resulted in a very slight rise in left anterior descending arterial flow and no change in great cardiac vein O2 saturation. This also relates the increase in flow through the left anterior descending artery to the O2 consumption of the left ventricle. However, in those experiments great cardiac vein O2 saturation was high prior to circumflex artery occlusion.

The question may be raised as to whether the increased aortic resistance imposed by tightening an aortic clamp to maintain a constant mean arterial pressure may have raised left ventricular oxygen consumption and there-
by resulted in the increase in left anterior descending arterial flow and the decrease in great cardiac vein O₂ content. The evidence fails to support such a contention since the determinants of myocardial O₂ consumption, namely, heart rate and arterial pressure, were relatively constant. Furthermore, because of the shortened systole resulting from occlusion of the circumflex artery (Fig. 3), the tension time index [a more reliable index of myocardial O₂ consumption (18)] is actually decreased. However, it is probable that the O₂ consumption of the contracting muscle supplied by the left anterior descending artery was increased during the functional failure of such a large portion of the left ventricle. This concept is supported by the rise in left ventricular diastolic pressure (Fig. 3).

The responses seen after coronary vasodilation by dipyridamole are those which would be expected if an increase in O₂ consumption occurred in the muscle supplied by the left anterior descending artery after occlusion of the circumflex artery. Since the vessels are dilated by the drug, the increase in O₂ consumption would be met by a greater extraction of oxygen and great cardiac vein O₂ saturation would decrease without significant change in left anterior descending arterial inflow. If an extensive border zone were perfused solely by the left anterior descending artery during circumflex occlusion, flows from the two arteries should have increased even though flow from the left anterior descending artery was already elevated by the dipyridamole. It is not possible from the present experiments to separate completely the possibility of border zone effects from the effects of increased metabolic activity in the nonischemic zone though the evidence favors the latter. Either mechanism could explain the arterial and venous flow and venous O₂ responses seen after occlusion of a coronary artery.

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