An Experimental Study on Intercoronary Reflexes

By Hsueh-Hwa Wang, M.D., Charles W. Frank, M.D., Donald M. Kanter, M.D. and René Wégría, M.D.

There is no evidence in the anesthetized dog that occlusion of one of the three coronary arteries leads to vasoconstriction in the vascular areas irrigated by the other two arteries. On the contrary, occlusion of one coronary artery appears to lead to a decrease in the resistance of the two adjacent vascular beds in most experiments. The mechanisms and the implications of this effect are discussed.

In 1939, Manning, McEachern and Hall reported that the mortality following coronary artery ligation was much greater in the unanesthetized than in the anesthetized dog. They proposed that this difference in the unanesthetized animal was due to the area of myocardium deprived of blood initiating impulses which induce a reflex constriction of the coronary bed unaffected by coronary artery ligation. Leroy, Fenn and Gilbert reduced the mortality due to ventricular fibrillation after coronary occlusion by administration of theobromine sodium acetate, theophylline ethylenediamine and atropine, and attributed the effect of these drugs to their coronary vasodilatatory effect, presumably preventing the reflex coronary constriction. Recently several workers restudied this problem and were unable to demonstrate the existence of a vasoconstrictor reflex after coronary occlusion. However, they studied the effect of occlusion of one coronary artery on only one of the other two coronary arteries and in relatively few experiments on few dogs. Furthermore although Opdyke and Selkurt concluded that their data did not provide acceptable proof of the hypothesis of reflex coronary vasoconstriction as a factor in sudden cardiac death after coronary occlusion, their "conclusion was reached in spite of the fact that there was evidence of vasoconstriction in two of the ten experiments." For these reasons, we have reinvestigated this problem by following continuously the effect of the ligation of one coronary artery on the simultaneous blood flow in the other two coronary arteries. Furthermore, the effect of the occlusion of each one of the three main coronary arteries on the blood flow in the others was studied successively. Finally, special care was taken not to disturb the innervation of the coronary vessels and a special cannulation technique, described below, was used to leave this innervation intact in at least one of the three main coronary beds.

METHODS

Eight mongrel dogs weighing 16 to 28 Kg. were anesthetized with 3 mg. of morphine sulphate/Kg., followed 30 min. later by intravenous injection of 0.25 ml./Kg. of an equal mixture of a 6 per cent solution of sodium pentobarbital and a solution containing 100 mg. of diallybarbituric acid and 400 mg. of urethane/ml. Under artificial respiration the left hemithorax was opened, the pericardium was incised and the heart suspended in a pericardial cradle. The right coronary artery was isolated about 1 cm. from its origin, the left common coronary artery at its origin and the left anterior descending artery in its middle third. An initial dose of 10 mg. of heparin/Kg. was followed every half hour by 5 mg./Kg. Blood derived from the right femoral artery was used to perfuse the right coronary, the left anterior descendens and left circumflex arteries via three rotameters. The circumflex coronary artery was perfused by inserting a cannula into the proximal end of the ramus descendens anterior and ligation of the left common coronary artery at its origin. The segment of the left anterior descending artery chosen for these upstream and downstream cannulations was selected so as not to occlude any side branches. Mean arterial blood pressure was obtained with a damped Gregg manometer connected to the cannula inserted into the right femoral artery. Continuous tracings of coronary blood flow and mean arterial blood pressure were recorded photographically.
Completion of the whole procedure was followed by a 5 to 10 min. stabilization period. The inflow tubing leading to each of the three coronary arteries was then occluded in turn, completely or partially, for 1 to 2 min. After each occlusion a recovery period was observed to allow all functions studied to return to control levels or at least to stabilize at a new level before another occlusion was carried out.

Results

Fifty occlusions were carried out on 8 dogs. The effect of the occlusion of one artery on the blood flow of one of the other two coronary arteries was studied 12 times and the effect of the occlusion of one artery on the blood flow of the other two arteries was recorded 38 times. The results observed are summarized in tables 1–3. The increases in flow as listed in the three tables refer to maximal increases which may occur at slightly different times in the different arteries.

Occlusion of the Right Coronary Artery. As can be seen in table 1, the right coronary artery was occluded completely 17 times in 8 dogs. The blood flow in the circumflex artery was recorded during 14 of these 17 occlusions, and the flow in the left anterior artery was recorded in all 17 experiments.

Occlusion of the right coronary artery produced an increase in the flow of the circumflex artery in 6 experiments (1, dog 1; 1 and 3, dog 3; 3, dog 5; 1 and 3, dog 8). Some increase in flow persisted for the duration of the occlusion in all 6 experiments, the mean arterial blood pressure falling in 3 of the 6 occlusions and remaining unchanged in the other 3. In experiment 1, dog 5 and 1, 3, dog 7, right coronary artery occlusion produced an initial increase in the circumflex artery flow, but after the first minute of occlusion, the mean arterial blood pressure fell markedly. Concomitant

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Exp. no.</th>
<th>Duration of occlusion (min.)</th>
<th>Mean arterial blood pressure (mm. Hg)</th>
<th>Right coronary artery flow before occlusion (ml/min.)</th>
<th>Circumflex coronary artery flow (ml/min.)</th>
<th>Left anterior coronary artery flow (ml/min.)</th>
</tr>
</thead>
</table>
with the fall in blood pressure, the left circumflex flow decreased below control level. In experiment 4, dog 2, circumflex artery flow increased initially, then decreased to its control level as the blood pressure fell. In 4 experiments (3 and 6, dog 1; 8, dog 2 and 1, dog 4), the circumflex artery flow was not modified by the right coronary artery occlusion although the blood pressure fell in all 4 experiments.

Occlusion of the right coronary artery increased the flow of the left anterior descending artery in 4 experiments (1 and 6, dog 1; 3, dog 3 and 1, dog 4), although the mean arterial blood pressure fell in all 4. In experiment 4, dog 2, the left anterior descending flow rose above control value, the blood pressure remaining at its control level, then the blood flow came back to its control value as the blood pressure decreased below control level. In the 2 experiments done on dog 7, the left anterior descending flow first was unchanged although the blood pressure fell, then, as the blood pressure fell markedly, the blood flow decreased slightly below control value. In the remaining 10 experiments (dogs 1-6 and 8), the blood flow in the left anterior descending artery remained unaffected by the right coronary artery occlusion although the blood pressure fell below control value in 7 of the 10 experiments.

**Oclusion of the Left Anterior Descending Coronary Artery.** As can be seen in table 2, the left anterior descending coronary artery was occluded completely 20 times in 8 dogs. Blood flow in the left anterior descending artery was recorded during 17 of these experiments.

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Exp. no.</th>
<th>Duration of occlusion (min.)</th>
<th>Mean arterial blood pressure (mm. Hg)</th>
<th>Left anterior coronary artery flow before occlusion (ml/min.)</th>
<th>Circumflex coronary artery flow (ml/min.)</th>
<th>Right coronary artery flow (ml/min.)</th>
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<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>Control: 113</td>
<td>62 (6)</td>
<td>2.5 (1.5)</td>
<td>18 (7.5)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1</td>
<td>Control: 121</td>
<td>2.5 (1.5)</td>
<td>18 (7.5)</td>
<td>25 (0)</td>
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<tr>
<td></td>
<td>7</td>
<td>1</td>
<td>Control: 120</td>
<td>2.5 (1.5)</td>
<td>18 (7.5)</td>
<td>25 (0)</td>
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<tr>
<td>2</td>
<td>2</td>
<td>1</td>
<td>Control: 115</td>
<td>20.5 (5)</td>
<td>27.5 (10.5)</td>
<td>30.5 (0)</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>1</td>
<td>Control: 110</td>
<td>20.5 (5)</td>
<td>27.5 (10.5)</td>
<td>30.5 (0)</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>1</td>
<td>Control: 98</td>
<td>17.5 (5)</td>
<td>27.5 (10.5)</td>
<td>30.5 (0)</td>
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<tr>
<td>5</td>
<td>1</td>
<td>1</td>
<td>Control: 92</td>
<td>17.5 (5)</td>
<td>27.5 (10.5)</td>
<td>30.5 (0)</td>
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<tr>
<td>6</td>
<td>1</td>
<td>1</td>
<td>Control: 92</td>
<td>17.5 (5)</td>
<td>27.5 (10.5)</td>
<td>30.5 (0)</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>2</td>
<td>Control: 124</td>
<td>9 (3)</td>
<td>27.5 (0)</td>
<td>27.5 (0)</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>2</td>
<td>Control: 122</td>
<td>9 (3)</td>
<td>27.5 (0)</td>
<td>27.5 (0)</td>
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although the mean arterial blood pressure fell in 13 of these 14 experiments. In experiment 9, dog 2, the circumflex artery flow increased initially although the mean arterial blood pressure fell, but the flow progressively fell to control level as the blood pressure fell markedly. In 2 experiments (3, dog 2; 4, dog 7), the circumflex artery flow remained unchanged during the occlusion of the descending artery although the mean arterial blood pressure fell.

In 4 of the 17 experiments during which the left anterior descending artery was occluded (2, dog 1; 2, dog 2; 4, dog 3; 4, dog 4), the right coronary flow rose above control level although the mean arterial blood pressure fell. In the other 13 experiments, the right coronary flow remained unchanged although the mean arterial blood pressure fell in 12 experiments; the blood pressure remained unchanged in the other experiment (2, dog 6).

Occlusion of the Circumflex Coronary Artery. The effects of circumflex coronary artery occlusion are summarized in table 3. The circumflex artery was occluded completely in 3 experiments on 2 dogs and partially in 10 experiments on 6 dogs. The effect of the circumflex artery occlusion on the right coronary artery flow was followed 10 times and its effect on the left anterior artery flow was recorded 13 times.

The right coronary flow increased and remained increased in 4 of 10 experiments although the blood pressure fell (5, dog 3; 5 and 7, dog 5; 5, dog 8). In 1 experiment, the right coronary flow rose although the blood pressure fell, then decreased to control level as the blood pressure fell further (7, dog 3). The right coronary flow remained unchanged in 4 experiments, the blood pressure falling in 2 experiments, (5, dog 7 and 7, dog 8), and remaining unchanged in the other 2 (10, dog 2 and 5, dog 4). Finally, the right coronary flow remained unchanged in 1 experiment, the blood pressure having fallen below control level, then, as the blood pressure fell further, the right coronary flow decreased below its control level (5, dog 1).

Occlusion of the circumflex artery augmented left anterior descending coronary artery flow in 10 experiments, the arterial blood pressure

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### Table 3: Effect of Partial or Complete Occlusion of Circumflex Coronary Artery

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Exp. no.</th>
<th>Duration of occlusion (min.)</th>
<th>Mean arterial blood pressure (mm Hg)</th>
<th>Circumflex coronary artery flow (ml/min.)</th>
<th>Left anterior coronary artery flow (ml/min.)</th>
<th>Right coronary artery flow (ml/min.)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Control</td>
<td>Change</td>
<td>Before occlusion</td>
<td>During occlusion</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Control</td>
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<td>Change</td>
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</table>

Note: Changes in blood pressure and flow are given relative to control values.
falling in 6 experiments (5 and 7, dog 3; 5 and 7, dog 5; 5 and 7, dog 8) and remaining unchanged in 4 experiments (6, 7 and 10, dog 2; 5, dog 4). In 1 experiment, the left anterior descending artery flow first rose, the blood pressure having fallen below control level, then the flow decreased to control level as the blood pressure fell further and very markedly below control (5, dog 1). In another experiment, the left anterior descending artery flow initially rose although the blood pressure fell, then the flow decreased progressively below its control level as the blood pressure fell very markedly below its control value (8, dog 1). Finally, in 1 experiment, the left anterior descending artery flow remained unchanged during circumflex artery occlusion although the arterial blood pressure fell markedly (5, dog 7).

**Discussion**

In 75 of the 88 observations made, when one of the three coronary arteries was occluded partially or completely for 1 to 2 min., the blood flow in the other two coronary arteries either rose while the mean arterial blood pressure remained unchanged or even fell, or the blood flow remained unchanged while the blood pressure fell below its control level. Therefore, it must be concluded that, in all these experiments, the occlusion of one artery decreased the peripheral resistance in the adjacent vascular beds. In another 6 observations, blood pressure and blood flow remained unchanged and the resistance of one of the two adjacent beds remained unchanged. In the remaining 7 observations, the blood flow remained unchanged or rose while the blood pressure fell, then, as the mean arterial blood pressure fell further, 16 to 61 mm. Hg below its control value, the blood flow decreased below its control value.* In none of the 88 observations did occlusion of one coronary artery ever left the flow in another one unchanged while the blood pressure rose. Therefore, the only conjunctures which would demonstrate an increase in the resistance of a vascular bed were never observed during these experiments. It must be concluded that under the experimental circumstances described, partial or complete occlusion of one of the three coronary arteries for 1 to 2 min. did not raise the peripheral resistance in the two adjacent beds irrigated via the other two coronary arteries. Whether the reflex vasoconstriction postulated by Manning, McEachern and Hall was abolished by anesthesia, the operative procedure, or both cannot be determined.

An analysis of the mechanism by which occlusion of one coronary artery leads, in most cases, to a decrease of the peripheral resistance in the adjacent vascular beds irrigated by the other two coronary arteries is of interest. It is known that once a coronary artery, the left anterior descending artery for example, is occluded and the intracoronary pressure distal to the occlusion has fallen, arterial blood is derived from one or both of the other coronary arteries into the left anterior descending bed. If the left anterior descending artery is cut open distal to the ligation, a back flow of arterial blood occurs which stops if the circumflex and the right coronary arteries are occluded. This proves that, at least in most dogs, there exist channels between the three vascular beds which are probably nonfunctioning when there is no pressure gradient between the different beds. Once the pressure falls within one bed, the pressure gradient so created drains blood from the adjacent arteries into the occluded artery when intercoronary channels exist. It would seem logical, for example, to ascribe the decrease of the peripheral resistance in the right and/or circumflex beds occurring after occlusion of the left anterior descending coronary artery to the decrease in pressure produced in the left anterior descending bed by the arterial occlusion. The resulting pressure gradient forces blood from the other beds into the left anterior descending bed via the intercoronary communications. Moreover, it seems probable that the pressure gradient between the vascular

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*Calculations of the coronary peripheral resistance were not made because of the questionable significance of such values in the case of the coronary circulation. Directional changes of the peripheral resistance were obtained when either flow alone or pressure alone changed or when flow and pressure changed in opposite directions.
bed whose artery is occluded and the adjacent beds is increased by the vasodilatation which is known to occur in ischemic areas of the myocardium. Finally, since even so brief an occlusion as 1 to 2 min. affects myocardial contraction, it seems likely that the extravascular support is reduced in the vascular bed whose artery is occluded, also accentuating the pressure gradient between the occluded vascular bed and the adjacent beds. A second factor may be responsible for the decrease in the peripheral resistance of—and eventually the increase in the blood flow of—the two non-occluded arteries when the third is occluded. As the ischemic area loses its contractility, the remainder of the ventricular myocardial mass compensates or attempts to compensate. It is probable that, even when the cardiac output and the arterial blood pressure fall, the work of the nonischemic portion of the ventricular mass is increased, inducing a decrease in the resistance of the coronary bed. This may well be a significant factor which induces a decrease in the resistance of one or both beds irrigated by the nonoccluded arteries. Whether this factor will affect the resistance in one or both nonoccluded arteries will depend on how much each one contributes to the irrigation of each ventricle under normal conditions. This is known to vary a great deal from dog to dog.

The observation that occlusion of one coronary artery reduces the resistance in the two adjacent vascular beds in most experiments does not completely rule out the possibility of reflex vasoconstriction. Indeed, it is conceivable, for example, that when the left anterior descending artery is occluded, the resistance in the right coronary artery bed decreases because it is in communication with the left anterior artery bed, in which the pressure has been lowered by the occlusion. It may well be that this decrease in the resistance of the "new" right coronary artery bed masks a constriction of the original right coronary bed and occurs despite this constriction. If such were the case, however, one would certainly still expect to observe an occasional increase in the resistance of the vascular beds adjacent to that of the occluded artery, especially when intercoronary communications happen to be poor or nonexistent. That no such increase has been observed makes it most improbable that vasoconstriction ever occurs after coronary occlusion, even in localized areas of the myocardium.

**Summary**

In the anesthetized dog, the blood flow was measured and recorded simultaneously and continuously in the right coronary artery, the left anterior descending coronary artery and the left circumflex coronary artery with three rotameters. When one of the three coronary arteries was occluded partially or completely for 1 to 2 min., in 75 of 88 observations either the blood flow in the other two arteries increased while the mean arterial blood pressure remained unchanged or decreased, or the blood flow remained unchanged while the blood pressure decreased. In 6 observations, blood flow and arterial pressure were unaffected by the occlusion. In 7 observations, the blood flow rose or remained unchanged as the arterial pressure fell below control, then as the blood pressure fell further, the flow decreased below control value. Every time the blood flow decreased, the mean arterial blood pressure fell.

These findings might be interpreted as indicating that under the present experimental conditions, there is no evidence that occlusion of one coronary artery leads to vasoconstriction in the vascular areas irrigated via the other coronary arteries. On the contrary, occlusion of one of the three coronary arteries appears to lead to a decrease in the resistance of the two adjacent vascular beds in most observations. Although these experiments do not rule out completely the possibility of reflex coronary vasoconstriction occurring in localized areas of the myocardium after coronary occlusion, this eventuality seems to be most unlikely.

**Summario in Interlingua**

In canes anesthesiate le fluxo de sanguine esseva mesurate e registrate continue e simultaneemente e per medio de tres rotametros in (1) le arteria dextero-coronaria, (2) le sinistre arteria coronari anetro-descendentis, e (3) le sinistre arteria coronari circumflexe. Quando un del tres arterias coronari esseva ocludite
parzial- o completamente durante 1 a 2 minu-
tas, le efecto in 75 ex 88 observationes esseva
(1) que le fluxo de sanguine in le altere duo
arterias se augmentava durante que le pression
medie del sanguine arterial remaneva stabile o
decresseva o (2) que le fluxo de sanguine re-
maneva stabile durante que le pression de
sanguine se reducve. In 6 observationes,
fluxo de sanguine e pression arterial non esseva
afh'cito per le occlusion. In 7 observationes, le
fluxo de sanguine se augmentava o remaneva
stabile durante que le pression arterial de-
creseva usque a infra le nivellos de controlo, e
postea, quando le pression de sanguine con-
tinuava decrescer, etiam le fluxo se reducveva
a infra le valores de controlo. Quandounque le
fluxo de sanguine decresseva, le pression medie
del sanguine arterial se reducveva.

Il pare possibile interpretar iste constatation-
nes como indication que sub le presente condi-
tiones experimental le occlusion de un arteria
coronari non resulta in vasoconstriction in le
areas vascular que es irrigate per le altere
arterias coronari. Contrarimente, il pare que le
occlusion de un del tres arterias coronarii resulta
in le majoritate del observationes in un reduc-
tion del resistentia in le duo adjacente systemas
vascular. Ben que iste experimentos non establi
categoricamente le impossibilitate del occurrentia
de reflexe vasoconstrictiones coronari in
areas localisate del myocardio post occlusion
coronari, un tal evento pare improbabilissime.

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