“Reverse Coronary Steal” Induced by Coronary Vasoconstriction Following Coronary Artery Occlusion in Dogs

MASSIMO CHIARIELLO, M.D., LAIR G. T. RIBEIRO, M.D., MICHAEL A. DAVIS, D.Sc., AND PETER R. MAROKO, M.D.

SUMMARY The phenomenon of “coronary steal,” i.e., the shunting of blood from ischemic to normally perfused areas of myocardium, has been described as an effect of the administration of several vasodilating agents. This study was performed to ascertain whether the reverse situation can be induced, i.e., whether vasoconstriction of the vessels supplying the nonischemic zone could increase the collateral flow to the ischemic area. In 16 open chest dogs, 15 and 30 min after occlusion of the left anterior descending coronary artery, epicardial electrograms were recorded and regional myocardial blood flow (RMBF) was measured with radiolabeled microspheres. Methoxamine was infused intravenously between 17 and 30 min, the mean arterial pressure being kept constant. The results indicate that while the coronary arterial flow to the normal myocardium fell from 90.6 ± 4.3 to 77.7 ± 3.2 ml/min/100 g (P < 0.01), the collateral blood flow to the ischemic area increased from 21.4 ± 3.5 to 41.0 ± 4.2 ml/min/100 g (P < 0.01), and thereby reduced acute myocardial ischemic injury. This favorable redistribution of blood flow might be considered a “reverse coronary steal.”

Phenomenon has been observed in the subclavian,1 aortoiliac,2 mesenteric3 and coronary4-12 vascular beds. In dogs with coronary artery occlusions or patients with ischemic heart disease, coronary vasodilator agents may increase the total coronary blood flow, but they may do this at the expense of reducing the collateral blood flow to the ischemic area already maximally dilated as a result of metabolic stimuli. This phenomenon has been described with carbocromen,2 dipyrindamole,4-6,9,10,11 isoproterenol10 and minoxidil.11 Since drugs which cause arterial dilatation in normal myocardium also reduce the arterial flow to ischemic areas, interventions which cause arterial constrict-
tion in normal myocardium might be expected to improve the blood flow to the ischemic areas. Accordingly, this study was designed to determine whether the administration of a coronary constrictor that reduced blood flow in the normal myocardium would increase the flow to the ischemic areas, thus producing a "reverse coronary steal."

**Materials and Methods**

Sixteen mongrel dogs weighing between 20 and 30 kg were anesthetized with sodium thiopental 25 mg/kg intravenously and ventilated with a Harvard respirator. A polyethylene cannula was placed in the carotid artery and connected to a Statham P23Db transducer to monitor arterial pressure. Lead aVp of the electrocardiogram was recorded continuously. A left thoracotomy was performed in the fifth intercostal space and the heart exposed and suspended in a pericardial cradle. The mid portion of the left anterior descending coronary artery was isolated from the adjacent tissue and occluded permanently with a silk suture. In eight of the dogs, 17 min after occlusion (control period) methoxamine (20.0 ± 0.5 μg/kg/min) was infused intravenously for 15 min, while mean arterial pressure (AP) was maintained constant by bleeding through a femoral artery catheter into a constant pressure chamber. This protocol was chosen in order to render the changes in coronary blood flow independent of changes in perfusion pressure which would rise with an increase of AP.

The regional myocardial blood flow (RMBF) and cardiac output (CO) were measured at 15 and 30 min after occlusion using 7-10 μ carbonized microspheres labeled with a gamma-emitting radionuclide (14Ce or 85Sr) according to the technique previously described. Before the injection, a 50 ml vial containing the microspheres suspended in a solution of 50% sucrose with two drops of Tween 80 added to avoid aggregation was ultrasonicated for 45 min and then mechanically agitated for an additional 5 min. For each measurement 1.5 × 10^6 of one type of labeled microsphere (selected randomly), suspended in an aliquot of 4 ml of the solution contained in the 50 ml vial, was injected over a period of 15 sec through a left atrial catheter, during the following 15 sec the catheter was flushed with 5 ml of saline. Random samples were taken from the vial after the injection for microscopic examination and these did not show aggregation of the beads. Simultaneously with the atrial injection a reference sample was collected from a femoral artery catheter using a 50 ml heparinized plastic syringe placed in a Harvard withdrawal pump operating at a constant speed of 15.3 ml/min. The collection of the reference blood sample lasted one minute, starting 15 sec before the beginning of the microspheres injection and ending 15 sec after the catheter flushing. No changes in aortic pressure or heart rate were observed during this procedure. Thirty-five minutes after the occlusion the heart was excised and 7 to 10 transmural biopsies each weighing 3 to 4 g were taken from the anterior and posterior ventricular walls. These biopsies contained all of the ischemic tissue as well as portions of the normal myocardium. Each biopsy was then divided into endocardial, middle and epicardial layers, and the radioactivity of each section and that of the reference sample measured in a gamma-scintillation well counter (Nuclear Chicago model 4233). Finally, the RMBF and the cardiac output were calculated as described by Utley et al. Since the goal of this study was primarily to examine changes in flow, the RMBF of the endocardial, middle and epicardial layers and the transmural blood flow were calculated separately for the ischemic and normal sites, the ischemic sites being defined as those with a blood flow below 50 ml/min/100 g. Transmural RMBF for each biopsy was calculated as a weighted mean of the corresponding endo, mid, and epicardial layer RMBFs.

Total vascular resistance (TVR) (in dyne x sec x cm^-2) was calculated according to the formula: TVR = (AP × 80)/CO where AP (mean arterial pressure) is in mm Hg and CO (cardiac output) in L/min. Coronary resistance (Cor Res) in dyne x sec x cm^-5/100 g of tissue, was calculated as follows: Cor Res = (AP × 80)/RMBF where RMBF (in L/min/100 g of tissue) was the mean blood flow of the non-ischemic sites.

Epicardial unipolar electrograms were recorded at 15 min and at 30 min after occlusion, i.e., just prior to the injection of microspheres, from 13 to 17 sites on the anterior left ventricular wall as previously described. The input impedance of the recorder amplifier was 100 megohms, and the frequency response of the system was ± 0.5 db from 0.14 to 70 Hz. The impedance of the electrode was maintained constant, as reflected in the reproducibility of the tracings. The electrode employed was a 15 mm4 copper cylinder with a saline soaked wick connected to the precordial V-lead and held by a cable perpendicular to the electrode, thus minimizing mechanical stress. Because of the large area of the electrode, small variations in location did not change the configuration of the

| Table 1. Hemodynamic and Electrocardiographic Changes |
|----------------|-------------------------------|----------------|----------------|
|                | Treated Dogs                  | After methoxamine |                |
| At 15 Minutes  |                               |                  |                |
|                 | 95.6 ± 6.2                    | 142.2 ± 7.7      | 10.5 ± 10^4    |
|                 | 150.1 ± 9.4                   | 142.2 ± 11.0     | 10.5 ± 10^4    |
|                 | 2.432 ± 0.433                 | 0.226 ± 1.374    | 0.8 ± 10^4     |
|                 | 3.625 ± 0.741 × 10^4          | 1.0 ± 1.121      | 1.1 ± 10^4     |
|                 | 9.3 × 10^4                   | 0.9 ± 0.575      | 0.8 ± 10^4     |
|                 | 3.4 ± 0.98                   |                  |                |
|                 | 4.9 ± 1.07                   |                  |                |
|                 | 110.0 ± 8.4                  |                  |                |
|                 | 5,651 ± 0.19                 |                  |                |
|                 | 10.5 × 10^4                  |                  |                |
|                 | 4.0 ± 1.0                     |                  |                |
|                 | 156.4 ± 0.19                 |                  |                |
|                 | 5,487 ± 0.19                 |                  |                |
|                 | 10.7 × 10^4                  |                  |                |
|                 | 4.6 ± 1.0                     |                  |                |
| At 30 Minutes  |                               |                  |                |
|                 | 106.9 ± 8.4                  |                  |                |
|                 | 155.5 ± 4.8                  |                  |                |
|                 | 1.621 ± 0.184                |                  |                |
|                 | 5,651 ± 0.660                |                  |                |
|                 | 10.5 × 10^4                  |                  |                |
|                 | 4.9 ± 1.0                     |                  |                |
|                 | 110.0 ± 8.2                  |                  |                |
|                 | 5,487 ± 0.176                |                  |                |
|                 | 10.7 × 10^4                  |                  |                |
|                 | 4.6 ± 1.1                     |                  |                |
| Abbreviations: AP = mean arterial pressure in mm Hg; HR = heart rate in beats/min; CO = cardiac output in L/min; TVR = total vascular resistance in dyne x sec x cm^-2; CR = coronary resistance in dyne x sec x cm^-5/g of myocardium; ST = average ST-segment elevation in mV. |
The sites, clearly recognizable for their relation with vascular crossings, were chosen in the area supplied by the occluded vessels as well as in regions of the left ventricle far away from this area. For each electrographic map, the average ST-segment elevation (ST) was obtained by dividing the sum of the ST-segment elevations in all sites by the number of sites. ST-segment elevations were measured from the T-P line to the J point. Nine percent of sites exhibited focal intraventricular conduction defect as reflected in QRS duration exceeding 0.065 sec and were excluded from the study. The other eight dogs did not receive any drug and served as controls; all measurements in these dogs were made at the same times as in the treated dogs.

Comparisons between values obtained at 15 and 30 min in the same dogs were made using Student’s paired t-test, and between treated and control dogs by Student’s t-test for group observations. Finally, an additional 12 open chest dogs were instrumented to evaluate the hemodynamic changes induced by the same dose of methoxamine. They were instrumented with ECG leads and cannulae in the left ventricle, aorta and left atrium for the recording of pressures.

**Results**

In the eight treated dogs the infusion of methoxamine with concomitant bleeding from 15 to 30 min after occlusion did not change the mean systemic arterial pressure (fig. 1, table 1). Systolic and diastolic pressures did not change (from 126.5 ± 9.3 to 125.4 ± 9.8 and from 79.9 ± 5.8 to 81.0 ± 5.4 mm Hg, respectively). Heart rate fell, but not significantly (fig. 1, table 1). Cardiac output decreased by 50.7 ± 6.1% (P < 0.01) (fig. 1, table 1). The calculated total peripheral resistance thus increased by 122 ± 22% (P < 0.01) (fig. 2, table 1). The transmural RMBF in the nonischemic zones, which was 90.6 ± 4.3 ml/min/100 g at 15 min after occlusion, was reduced by the intervention to 77.7 ± 3.2 ml/min/100 g (P < 0.01) at 30 minutes (fig. 3 and table 2). The analysis by layer is shown in figures 3 and 4 and table 2. In the normal myocardium the calculated coronary resistance per gram of tissue increased in all three layers and when calculated for the transmural samples it in-

**Figure 1.** Effect of vasoconstriction and simultaneous bleeding on mean arterial pressure (AP), heart rate (HR), cardiac output (CO) and average ST-segment elevation (ST). The striped columns represent the control values at 15 min, the dotted columns the values at 30 min during vasoconstriction. All values are mean ± 1 standard error. * = different from control, P < 0.05. ** = different from control, P < 0.01.

**Figure 2.** Effect of methoxamine plus bleeding on total vascular resistance (TVR) and coronary resistance (CR). Note the increase of both parameters following the intervention. * = different from control, P < 0.05. ** = different from control, P < 0.01.


The administration of methoxamine (table 2).

As a result of the increase in the collateral blood flow to the ischemic areas, the average ST-segment elevation, which was 1.3 ± 0.5 mV 15 min after the occlusion, fell significantly during the intervention to 2.0 ± 0.3 mV (P < 0.02) (figs. 1 and 6, table 1), showing a reduction in the magnitude of the acute myocardial ischemic injury.

In the eight control dogs the ΔP, HR, CO, ST, RMBF, and total vascular and coronary resistances did not change significantly between 15 and 30 min after the occlusion (tables 1 and 2), showing that there is no spontaneous change in these parameters.

In the 12 dogs evaluated for changes in hemodynamics,
methoxamine infusion and simultaneous bleeding resulted in unaltered aortic and left ventricular systolic pressures (127 ± 6 to 125 ± 6 mm Hg), aortic diastolic pressure (107 ± 7 to 108 ± 7 mm Hg), left ventricular end-diastolic and atrial mean pressures (5.3 ± 1.5 to 4.4 ± 1.6 mm Hg) and heart rate (161 ± 6 to 156 ± 6 beats/min). In contrast, max LV dp/dt fell significantly by 20.3% from 2,331 ± 133 to 1,857 ± 147 mm Hg/sec (P < 0.01).

**Discussion**

A fundamental aim in the treatment of ischemic heart disease is to improve the balance between oxygen supply and demand in the ischemic region of the heart.16, 19-22 This may be achieved either by increasing the heart’s oxygen supply (i.e., perfusion) or by reducing its oxygen requirements. Coronary artery bypass grafting23 is a typical example of the former approach and propranolol administration of the latter.24-26 Coronary vasodilators were introduced with the hope that they would increase oxygen supply by dilating the narrowed vessels; however, their role is controversial because they may have multiple and complex effects. They may, for example, affect the ischemic zone not only through their action on the coronary arteries themselves but also through their peripheral vascular effects. Their ability to reduce systemic arterial pressure and pulmonary vascular resistance may reduce afterload and preload. Drugs such as nitroglycerin may also reduce preload by causing pooling of blood in the venous system. Such a decrease in afterload and/or preload reduces myocardial oxygen requirements and this has been considered important for limiting the extent of ischemia.27-30 Moreover, the effects of the coronary vasodilators on the coronary bed itself is not uniform. Diverse effects have been shown on the degree of ischemia indicating that coronary vasodilators are pharmacologically a heterogeneous group of drugs.31-33

Vasodilators that act on the proximal conductance vessels are considered beneficial,34-36 while those that act on the peripheral resistance vessels are thought to be detrimental37 because they produce a redistribution of flow similar to a coronary steal. We postulated that coronary constrictors

---

**Figure 4.** Effects of coronary constriction on regional myocardial blood flows (RMBF) in endocardial (endo), middle (mid) and epicardial (epi) layers of the normally perfused sites. ** = different from control, P < 0.01. Note the reduction of flow after vasoconstriction.

**Figure 5.** Effects of coronary constriction on regional myocardial blood flows (RMBF) in endocardial (endo), middle (mid) and epicardial (epi) layers of the ischemic sites. Note the marked increase of collateral flow to these ischemic zones following the vascular constriction of the normal areas. ** = different from control, P < 0.01.
that act on resistance vessels are beneficial while constrictors that act on conductance vessels are harmful. Accordingly, the goal of the present study was to ascertain whether reverse coronary steal can be induced by coronary constriction in the normal part of the myocardium. The constant infusion of methoxamine while the systemic pressure was kept constant resulted in a reduction of regional myocardial blood flow to the normal areas. This reduction in flow can be ascribed both to the lowering in myocardial oxygen consumption and to the presumed constrictive action of the drug on the coronary arterioles. In contrast, regional myocardial blood flow in the ischemic areas increased (fig. 7). The failure of methoxamine to constrict the arteries in the ischemic areas may be explained either by a reduced amount of the drug reaching the underperfused zones or, more probably, by the more powerful metabolic vasodilation induced by the ischemia itself. Collateral vessels may have their origin at the level of the arterioles. When the pressure in large arteries is maintained constant despite infusion of vasoconstrictors, the pressure at the level of the arterioles is significantly increased. This increase in perfusion pressure at the origin of the collateral vessels may therefore be responsible for the reverse coronary steal. This augmentation of collateral flow achieved through the induction of a reverse steal phenomenon was accompanied by a significant reduction in acute myocardial ischemic injury as reflected by the change in the average ST-segment elevation.

The possible multifaceted effects of methoxamine on regional myocardial blood flow in the normal areas and the consequent reverse coronary steal should be analyzed closely since they may help to explain the salutary effects of other agents which have similar general effects. Methoxamine, as a result of alpha receptor stimulation, causes coronary constriction. However, a reduction in myocardial oxygen consumption will also reduce coronary flow in the normal myocardium. In the hemodynamic experiments performed in this study, heart rate, preload and afterload did not change following drug administration; however, left ventricular dp/dt decreased by 20%, presumably resulting in lower myocardial oxygen consumption. This fall in dp/dt can be induced by a beta blocking effect of methoxamine. Thus, at least two factors could have contributed to the coronary vasoconstriction: the direct effect of alpha receptor stimula-

Figure 6. Simultaneous changes in average ST-segment elevation (ST) and ischemic transmural flow. The coronary constriction produced an increase in collateral flow and consequently a reduction in ST.

Figure 7. Schematic representation of the hypothesis of reverse coronary steal. The left panel illustrates the distribution of flow following coronary artery occlusion. Blood flow in the nonoccluded vessel is directed mainly to the normal myocardium (larger arrow) which exhibits a normal resistance; less blood flow (small arrow) is directed through the collaterals to the ischemic area (diamond shape) where the coronary resistance is low (loose spring). The right panel illustrates the alteration due to methoxamine accompanied by bleeding. There is an increase in coronary resistance in the normal myocardium (tight spring), producing a decrease in flow to the normal myocardium (arrow reduced in size). Consequently there is an increase in blood supply to the ischemic zone (small arrow increases) through the collaterals and the extent of myocardial injury is reduced (smaller diamond).

The authors gratefully acknowledge the technical assistance of Mr. Daniel White, Mr. Joseph Gannon and Ms. Alice Carmel as well as the secretarial assistance of Ms. Merrilee Spence.

References
REVERSE CORONARY STEAL/Chiariello et al. 815

"Reverse coronary steal" induced by coronary vasoconstriction following coronary artery occlusion in dogs.
M Chiariello, L G Ribeiro, M A Davis and P R Maroko

Circulation. 1977;56:809-815
doi: 10.1161/01.CIR.56.5.809

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1977 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/56/5/809

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation 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 is online at:
http://circ.ahajournals.org//subscriptions/