Intercoronary Reflex

DEMONSTRATION BY CORONARY ANGIOGRAPHY

By Santiago V. Guzman, M.D., Edward Swenson, M.D., and Malcolm Jones, M.D.

There is a fairly widespread belief that injury to an artery leads to peripheral vasospasm, which sometimes involves nearby vessels as well as the one directly injured. This has led to several attempts to determine whether injury to a coronary artery, by ligation or embolization, might cause spasm of the embolized vessel distal to the point of injury or constriction of other nonembolized branches of the coronary arterial system. However, no one has obtained clear evidence of such a response. Gregg was unable to demonstrate reflex vasoconstriction in one coronary artery or branch when another was ligated. Wang, Frank, Kanter, and Wegria followed continuously the effect of ligation of one coronary artery while perfusing simultaneously the other two coronary arteries. They were unable to demonstrate reflex vasoconstriction; indeed, occlusion of one coronary artery appeared to lead to a decrease in the resistance of the unaffected vascular bed. These experiments were performed in open-chest preparations, and the coronary circulation and its nerves were modified by ligation of one of its coronary arteries.

Recently, West, Kobayashi, and Guzman have devised a technique for catheterization of one or two coronary arteries in the anesthetized dog, without opening the thorax, by passing a long slender tube down a carotid artery into the coronary ostium and thence into either the left anterior descending or left circumflex coronary artery. They have used this tube for localized administration of drugs and for selective coronary angiography. They found it possible to demonstrate by coronary angiography drug-induced constriction and dilatation of the coronary vessels. The technique has the following advantages: (1) it permits selective placement of emboli in branches of the coronary artery rather than in the arch of the aorta near the coronary ostia; (2) the procedure is done with the thorax closed; and (3) most important of all, there is no damage to perivascular nerves such as inevitably results from tying a ligature about a cannulated coronary vessel. Because of these advantages, we thought it worthwhile to reinvestigate, by selective coronary catheterization, the question of coronary vasoconstriction induced by embolization.

**Methods**

Twenty-eight adult mongrel dogs, weighing 20 to 25 Kg., were anesthetized with morphine (3 mg./Kg.) and 0.25 ml./Kg. of a mixture composed of equal volumes of Dial-urethane solution (100 and 400 mg./ml., respectively) and pentobarbital sodium (60 mg./ml.). We catheterized the anterior descending or the circumflex branch of the left coronary artery; or both, under fluoroscopic guidance using the special coronary arterial catheter previously described.

We used 0.2 to 0.4 ml. of a well-shaken 1 percent suspension of lycepodium spores in saline as the embolizing agent and flushed this with 2 ml. of arterial blood.

Coronary arteriography was used to detect: (1) the effect of embolization on the coronary artery into which the spores were injected and (2) the effect on nonembolized branches of the same artery. For (1), we introduced only one catheter and injected first the contrast medium, then the emboli and a flushing injection, and then contrast medium again. For (2), we introduced two catheters, one into the circumflex and the other into the left anterior descending branch; we used one for injection of emboli and the other or both for injection of the contrast medium.
Coronary arteriograms of the anterior descending branch before and after embolization with lycopodium spores. The location of the catheters (in each picture): (left) left anterior descending branch, (middle) left ventricle, and (right) aorta. The needle is an ECG electrode inserted hypodermically over the precordium. The volume of radiopaque substance (1.5 ml.) injected was the same in all the pictures. At the left is the control angiogram (blood pressure, 140/95; heart rate, 85). The middle picture was taken 50 seconds after embolization of the same coronary vascular bed with 0.2 ml. of 1 per cent lycopodium spores (blood pressure, 90/80; heart rate, 100). Note the marked diminution of the size of the vascular bed and reflux of the injected radiopaque substance into the left circumflex branch. The picture on the right was taken five minutes after embolization (blood pressure, 140/95; heart rate, 85). Note the return of the coronary vascular pattern to the pre-embolization picture.

The contrast medium used was 85 per cent methylglucamine diatrizoate (Cardiografin).\* We injected enough to outline the entire vascular bed studied; this varied from 1.5 to 4.0 ml. in different animals. In any single experiment, the same amount of Cardiografin was injected at the same rate each time; this was usually 1 ml./sec.

In some experiments, routine roentgenograms were made; in others, successive serial films were exposed; and in others, an image intensifier was photographed using 16- or 35-mm. motion picture film running at 48 to 60 frames per second.

Coronary arterial resistance was estimated in three ways: (1) by noting changes in the vascular pattern on the arteriogram taken after embolization; (2) by observing whether reflux occurred during injection of the contrast medium—in the control period, minimal or no reflux occurred with the standard injection of Cardiografin; and (3) by counting the number of frames on the cine-angiogram between the time of injection of the contrast substance and its disappearance from the coronary arterial tree. The third method gave highly reproducible figures in the control period when the dye was injected four times, at two-minute intervals, using constant rate and volume of injection (see fig. 6).

Femoral arterial blood pressure was measured using a Statham strain-gauge transducer attached to a multichannel photographic recorder (Electronics for Medicine). We monitored the electrocardiogram continuously on the same recorder, using a standard lead II, or a precordial lead (V₃).

In four dogs, 0.1 mg./Kg. of atropine was administered intravenously, before placing emboli in the coronary arterial tree.

**Results**

**ROUTINE ANGIOGRAMS OF THE EMBOLIZED CORONARY BRANCH**

The roentgenograms made immediately following embolization with lycopodium spores indicate that Cardiografin is a mild coronary vasodilator.*

*Generously supplied by Mr. S. C. Sutton, E. R. Squibb & Sons, San Francisco, California. Quantitative measurements of coronary blood flow indicate that Cardiografin is a mild coronary vasodilator.*

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Coronary angiograms of the circumflex branch of the left coronary artery before and after embolization with lycopodium spores. The amount of contrast substance injected (2 ml.) was the same in all the pictures. On the left is the control angiogram (blood pressure, 160/100; heart rate, 95). In the center picture, note the marked decrease in the size of the coronary vascular bed with reflux of the radiopaque material into the aorta one minute after embolization of the same site with 0.3 ml. of 1 per cent lycopodium spores (blood pressure, 90/85; heart rate, 100). On the right, 1-1/2 minutes later (blood pressure, 90/86; heart rate, 100), the coronary vascular pattern has reappeared, but some of the finer branches are not seen, and evidence of increased vascular resistance is still present (reflux of dye into the aorta). Note that the blood pressure in the second and third pictures is identical (shock level) so that the level of blood pressure does not account for the failure to visualize the coronary vascular bed in the middle picture.

showed a marked decrease in the size of the coronary vascular bed (note "cut-off" pattern, middle angiogram (figs. 1 and 2). Because the control arteriograms were taken when the systemic blood pressure was normal, and the postembolization arteriogram was taken during a period of hypotension, we considered the possibility that the reduction in size of the coronary vascular bed was due to a lower blood perfusion pressure. However, there was good visualization of the coronary vessels during hypotension induced by hemorrhage. One might logically conclude that the immediate postembolization pattern was due solely to mechanical blockade of small vessels by the lycopodium spores. However, within five minutes, the "cut-off" vascular pattern was replaced by a near-normal pattern (right, figs. 1 and 2). Since the spores (either as aggregates or singly) were too large to be flushed through the coronary capillary bed, the immediate "cut-off" pattern may well represent spasm of large vessels in the embolized coronary branch. The spasm apparently relaxed within four to five minutes and then permitted filling of vessels down to mechanically blocked arterioles (postmortem studies of the embolized myocardium showed that the spores occluded, wholly or in part, arterioles 40 to 300 μ in diameter).6

Another possible explanation is that mechanical obstruction of fine vessels prevented good visualization of larger, proximal vessels. This was tested by injecting 0.2 ml. of metallic mercury into a coronary artery and then injecting Cardiografin. Figure 3 shows complete filling of the vessel with the opaque medium to the point of occlusion by the intrarterial mercury; we obtained similar results in two additional dogs.
FIGURE 3
Left picture shows the coronary arteriograms of the anterior descending branch after embolization with metallic mercury (1.5 ml.). On the right, 1.5 ml. of the radiopaque dye was injected into the same site. Note the demonstration of the continuity of the vascular pattern up to the site of occlusion.

ROUTINE ANGIOGRAMS OF THE NONEMBOLIZED CORONARY BRANCH
In six dogs, angiograms of the nonembolized branch showed a marked reduction in its caliber when emboli were injected selectively into another branch (fig. 4). Histological studies of the heart showed that lycopodium spores were present only in the distribution of the embolized branch.

CINEMATOGRAPHIC STUDIES
We placed a single catheter in a coronary vessel in 10 dogs and two catheters in coronary arterial branches in another 4 dogs and studied these animals by cinefluorography. After coronary embolization, in both the embolized vessels and, when studied, the nonembolized vessel, there was (1) marked decrease in the size of the coronary vascular bed during systole and diastole, (2) considerable delay in clearance time as indicated by the number of frame counts before the Cardiografin disappeared, and (3) considerable reflux of the contrast material into the other coronary artery or aorta (fig. 5).

EMBOLIZATION AFTER ATROPINE
Previous studies showed that atropinization prevented much of the hypotension that usually occurs after selective coronary arterial embolization. We suspected that atropine might be acting by preventing coronary vasospasm.

Figure 6 shows that the "run-off" time of Cardiografin in the atropinized, embolized dogs was increased only 35 per cent (mean of four dogs) as compared with 190 per cent increase in six nonatropinized, embolized dogs.

Discussion
We realize that coronary arteriography, even when recorded continuously by motion picture photography of the fluoroscopic screen, does not provide a measure of coro-
Combined catheterization of the anterior descending and circumflex branches of the left coronary artery. The catheter in the anterior descending branch is directed to the sternum and the left circumflex catheter points to the vertebral column. The needle is an ECG electrode inserted subcutaneously over the precordium. The catheter in the anterior descending branch was used for dye injection (1.5 ml.), while the left circumflex catheter was used for injection of the embolizing agent. The catheter in the anterior descending branch was used for dye injection (1.5 ml.), while the left circumflex catheter was used for injection of the embolizing agent. On the left is the control arteriogram (blood pressure, 150/100; heart rate, 100). After embolization of the left circumflex branch with 0.3 ml. of 1 per cent lycopodium spores, repeat injection 30 seconds later of the same amount of dye into the anterior descending branch (middle picture) showed a marked decrease in the size of the nonembolized vascular bed with reflux of the dye into the aorta (blood pressure, 90/80; heart rate, 110). The picture on the right was taken two minutes after the embolization, showing reappearance of the smaller branches of the coronary vessels. However, there is still evidence of increased resistance to flow as shown by the reflux of the dye into the left circumflex branch (blood pressure, 140/95; heart rate, 105). Postmortem studies of the heart revealed that the embolizing agent was present only in the distribution of the left circumflex artery.

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One catheter is in the left anterior descending branch and another in the left circumflex branch. Left picture is control visualization of both coronary branches after injection of 4 ml of contrast substance (with T type of connection from injection syringe) (blood pressure, 123 mm Hg; heart rate, 95). Middle picture was taken 40 seconds after embolization of the left circumflex branch with 0.3 ml of lycopodium spores (blood pressure, 60 mm Hg; heart rate, 150). Picture on right was taken 10 minutes after death. (Pictures taken two and five minutes after death still showed evidence of "coronary spasm.") Histological studies of the heart showed the spores were localized in the distribution of the left circumflex branch.

Graph showing the mean changes in the cinefluorographic frame count following initial embolization in normal and atropinized dogs. The vertical lines indicate 2 standard deviations of the values obtained in the first minute following embolization. Note the marked increase of frame count (indicating prolonged disappearance time of the injected contrast substance) in both the embolized and nonembolized branches in the normal dogs. Also note the return of the disappearance time to near normal two to four minutes following embolization.

Summary

The effect of coronary embolization on the coronary vascular bed was studied in the intact anesthetized dog utilizing the technique of coronary artery catheterization without opening the thorax. Two coronary arterial catheters were inserted via the carotids, one into the anterior descending branch and the other into the circumflex branch of the left coronary artery. Coronary vascular visualization was accomplished by routine roentgenography and by cinefluorography (using an image intensifier and 16- and 35-mm. motion picture film at 48 to 60 frames/sec.) of the heart after injection of a radiopaque dye into a coronary vessel. The results following coronary embolization showed that in both the embolized and nonembolized coronary vessels there was: (1) marked decrease in the size of the coronary vascular bed, (2) reflux of flow, pressure, and resistance in one isolated coronary arterial branch while embolizing another; these studies, technically difficult because of the necessity to avoid coronary artery ligatures, are now in progress.
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the injected contrast substance into the other coronary artery or into the aorta, (3) considerable delay in the disappearance time of the injected radiopaque material. Under the conditions of our experiments, these results can be interpreted as evidence of a generalized left coronary vasoconstriction following embolization of a branch of the left coronary artery. This was prevented to a great extent by the prior injection of atropine.

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Addendum

Since this paper was submitted for publication, we have been privileged to read a manuscript by J. W. West, "Cardiovascular Effects of Selective Coronary Embolization with Special Reference to Coronary Reflexes and Acute Myocardial Ischemia."

Using similar techniques, West concluded that constriction occurred in neither the embolized vessel nor in its nonembolized branches. Since his angiograms of the embolized vessels are similar to ours ("cut-off" pattern of an embolization followed in a few minutes by good visualization of the embolized vessels), the difference is one of interpretation; we cannot escape the conclusion that there was vasoconstriction in his experiments as well as ours. The emboli were still present in the vessels (shown in our studies by histological sections of the heart), yet the initial " blanking out" of vessels was followed in a few minutes by reappearance of a vascular pattern identical to the control. This cannot be due to opening of new channels since the "control" and "recovery" vascular patterns can be superimposed.

West's failure to observe reflex obstruction of nonembolized branches may be due to small but critical differences in technique: amount and type of contrast material injected, injection time and pressure of the opaque medium, dose of lyceopolonium spores, timing of roentgenograms, or to the use of single films instead of cinefluorography. The most convincing evidence of reflex spasm (cinefluorography) can be presented in print quantitatively only as a measurement of clearance time, as in our figure 6.

References

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