Effects of Selective Coronary Embolization on Coronary Blood Flow and Coronary Sinus Venous Blood Oxygen Saturation in Dogs

WITH SPECIAL REFERENCE TO CORONARY REFLEXES

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Reflex mechanisms affecting the coronary circulation have been postulated and described as participating in the profound fall in blood pressure frequently attending cardiogenic shock following acute coronary occlusion. The reflex mechanisms suggested as being responsible for potentiating the cause of sudden death in coronary artery disease are: (1) an intercoronary reflex, which is believed to produce reflex coronary vasoconstriction in the nonoccluded bed during acute coronary occlusion of one branch, thereby contributing to the shock condition, and (2) the Bezold-Jarisch reflex, which produces a decrease in cardiac output and vasodilation, thus initiating a greater fall in blood pressure than would otherwise be expected from occlusion of one coronary artery alone.

Existence of a reflex between the coronary arteries has been under continuous study since Manning and his colleagues reported that the mortality rate following coronary occlusion can be reduced by sympathectomy, vagotomy, atropine, coronary vasodilators, and anesthesia. Such results alone do not prove that acute coronary occlusion is accompanied by a reflex vasospasm of adjacent coronary arteries. Demonstration of reflex coronary vasoconstriction demands, as aptly stated by Opdyke and Selkurt, unequivocal evidence that coronary flow is reduced in one of the other arteries adjacent to the occluded artery, and that the reduction in coronary flow is due to vasoconstriction which is sufficient to reduce blood flow to impair fatally the function of the heart. Attempts to obtain such information have been recently undertaken by several investigators, with consistently negative results.

Meilman and Krayer, as well as Schimert, suggested the possible participation of the Bezold-Jarisch reflex in this shock condition. However, experiments by Levy and Frankel, and by Agress and associates, indicate that the Bezold-Jarisch reflex plays no part in coronary shock. Negative results in such experiments are subject to the objection that the insertion of cannulae into coronary arteries may interrupt important nerve pathways, as Aviado, Ling, and Schmidt have found it to do in corresponding experiments on the pulmonary arterial system. To obviate this difficulty, one of us (J.W.W.) developed techniques for catheterization and/or cannulation of the coronary arteries (left circumflex, left anterior descending, right coronary) in the dog without opening the chest.

To produce a controllable coronary occlusion, we used the technique employed by Hamburger, Priest, and Bettman in 1926, who described a graded type of acute and chronic myocardial ischemia following embolization by lycopodium spores in dogs. By injecting lycopodium spores through cathe-
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ters positioned in a coronary artery we could fulfill the criteria of preserving vascular and nervous continuity while eliciting myocardial ischemia of controllable severity.

In the following pages, studies of embolization are reported on: (a) coronary blood flow and coronary sinus venous blood oxygen saturation in normal dogs; (b) coronary blood flow following cardiac denervation and adrenalectomy; and (c) search for intercoronary reflexes as demonstrated by selective coronary and angiography and coronary arterial perfusion.

Methods

Studies of coronary blood flow and coronary sinus venous blood oxygen saturation in normal dogs were made in 49 normal adult mongrel dogs, weighing 17 to 30 Kg., under pentobarbital sodium anesthesia (30 mg./Kg., I.V.). The trachea was cannulated and respirotions were recorded by a pneumograph with the aid of fluoroscopy. A carotid catheter (no. 7), with an inflatable balloon attached to its tip, was placed in the descending aorta just above the diaphragm, via a femoral artery. The balloon could be inflated when it was desired to obstruct flow in the descending aorta. Glass cannulae inserted into brachial and femoral arteries were attached to a single dampered mercury manometer to record mean arterial blood pressure. A polyethylene catheter was placed in a femoral vein for intravenous injections, and cannulation of the coronary sinus was accomplished in the intact animal with a special coronary sinus cannula (modified Morawitz cannula) inserted via the external jugular vein under fluoroscopic guidance. The cannula was provided with multiple openings at the tip, and with an inflatable balloon to secure its position in the coronary sinus. The coronary sinus outflow was directed into a calibrated chamber connected to a low resistance recording spirometer. As the blood from the coronary sinus collected in the calibrated chamber, it was timed for measured volumes to secure a quantitative calibration of the record traced on the kymograph by the recording spirometer. The blood in the calibrated chamber was emptied by a siphon mechanism into the reservoir of a Dale-Schuster pump, which returned the blood to the animal via a femoral vein. Duplicate control flows in the same animal returned the blood to the animal via a femoral vein. Duplicate control flows in the same animal varied less than 5 per cent and the average flow measurements by this technique were comparable to those measured by the nitrous oxide method. Simultaneous anaerobic sampling of coronary sinus venous blood and femoral arterial blood was accomplished through individual manifolds attached to indwelling polyethylene catheters in the coronary sinus and a femoral artery. Mannite (10 mg./Kg.) was administered intravenously as an anticoagulant.

In the first 38 dogs, coronary artery embolization was accomplished by Aguress’ method, i.e., injection through a metal catheter with an inflatable tip inserted via a carotid artery and placed in the ascending aorta near the coronary ostia with the aid of fluoroscopy. During these studies, the technique for selective coronary artery catheterization was developed.

Blood gas contents of oxygen and carbon dioxide were determined by the manometric method of Van Slyke and Neill. Blood samples were also analyzed for oxyhemoglobin by the Beckman spectrophotometric method. Electrocardiograms were recorded through standard limb leads or precordial lead (V5) to determine heart rate and changes in electrical activity.

The standard experimental procedures began with control recordings of coronary sinus venous outflow, mean arterial blood pressure, respirations, heart rate, electrocardiographic activity, and collection of arterial and coronary sinus venous blood samples for analysis. Following the control period, an injection of a 5 per cent suspension of lycopodium spores was made in the ascending aorta just proximal to the coronary ostia (39 experiments) or (in 11 experiments) of 1 per cent suspension directly into the left circumflex or left anterior descending coronary artery. The observations were then repeated, and at the time of maximal coronary sinus blood flow response, a simultaneous anaerobic collection of arterial and coronary sinus venous blood was made.

To determine the effect of coronary embolization on coronary blood flow following cardiac denervation and adrenalectomy, seven animals were subjected to one or more of the following denervation procedures: (a) bilateral thoracic sympathectomy, (b) bilateral vagotomy, (c) bilateral lumbar sympathectomy and splanchnic division, (d) bilateral adrenalectomy, and (e) spinal cord transection (C6 to C7). In addition, adrenal vein ligation was performed in another animal. The preparation and study of these surgically operated animals were largely undertaken by one of us (F.S.A.) In these experiments, coronary embolization was accomplished by indirect (aortic) injection, since a selective coronary arterial injection technique was still in the developing stage at the time.

In the animals subjected to bilateral thoracic sympathectomy from the stellate ganglia through T9 to abolish myocardial sympathetic innervation, and in those undergoing bilateral lumbar
Effects of a small dose (0.1 ml. of 5 per cent suspension) of lycopodium spores injected into ascending aorta near coronary ostia. The responses plotted in the graph represent the average responses observed in 14 animal preparations during embolization, on coronary venous oxygen saturation (%), coronary sinus blood flow, heart rate, and mean arterial blood pressure. Note the initial marked decrease in coronary sinus blood flow and a slight increase in heart rate during the slight decrease in blood pressure. Immediately following the initial responses, there occurred a marked increase in coronary blood flow accompanied by a marked increase in coronary venous oxygen saturation. At the same time, heart rate and blood pressure returned to control levels.

In other preparations, attempts to establish the existence of a reflex capable of eliciting angiospasm in coronary arteries, when one coronary arterial branch is embolized, occluded, or constricted, were made by utilizing direct coronary artery catheterization for contrast—roentgenological evaluation of the behavior of the coronary circulation. In addition to this, another experimental approach was employed for securing further evidence on this point by determining changes in coronary vascular resistance, estimated by changes in perfusion pressure while maintaining inflow constant in the major coronary arteries.

The studies utilizing contrast—roentgenography were performed on 34 normal adult mongrel dogs weighing 20 to 30 Kg., lightly anesthetized with a combination of equal parts of pentobarbital sodium veterinary solution (60 mg./ml.) and Diatame solution (100 and 400 mg./ml.), given intravenously on the basis of 0.25 ml./Kg. of the mixture after a previous intramuscular injection of morphine (3 mg./Kg.). The major branches of the coronary arteries (left anterior descending, left circumflex) were catheterized both alone and in combination under fluoroscopic guidance via a carotid artery with the special coronary artery catheter (West) already described. In addition, a special occluding catheter with an enlarged metal tip was designed for the twofold purpose of obstructing flow into a coronary artery and injecting contrast medium for angiographic demonstration of the vessel before and after occlusion. Systemic blood pressure (via a femoral artery) was measured by a Statham transducer manometer, and was recorded by a direct-writing Sanborn polyviso recorder. The electrocardiogram was continuously monitored in the same recorder, using conventional precordial and limb leads. The effects of embolization by lycopodium spores (0.1 ml. of a 1 per cent suspension), were studied on the coronary vascular bed by means of roentgenograms made after injection of a fixed amount of radioopaque material (2.0 to 5.0 ml.) before and immediately after the embolizing agent. Sodium and methylglucamine (Renografin®) diatrizoates (76 per cent) were the contrast mediums used in this study and the same general procedures, as previously described, were followed.

In this study, the following were undertaken:

*Generously supplied by the Ciba Pharmaceutical Products, Inc., Summit, New Jersey.
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(a) the effect of embolization on the embolized and adjacent nonembolized branches; (b) the effects of various autonomic blocking agents, atropine (0.1 to 1.9 mg./Kg.), tetrathylammonium (TEA) (1.0 to 10 mg./Kg.), and hexamethonium bromide (1.0 to 10 mg./Kg.) on the initial response of embolization; (c) the ability of various coronary vasodilator agents, nitroglycerin (5.0 to 40 mg./Kg.) and sodium cyanide (1.5 mg./Kg.), to alter the initial response of embolization with the vasoconstrictor response of pitressin; and (d) a comparison of the initial effect of embolization with the vasoconstrictor response of pitressin.

(b) Two dogs in which the main branches of the left coronary artery (anterior descending, left circumflex) were perfused separately; (c) three dogs in which the left anterior descending branch (left anterior descending, left circumflex) by a special occluding catheter. In all experiments, observations were made during spontaneous breathing of room air.

In those studies utilizing controlled perfusion of the coronary arteries, the experiments were performed in eight normal dogs anesthetized with the same combination anesthesia. Cannulation and perfusion of the coronary arteries were accomplished through the special catheters without opening the chest or interrupting perivascular nerves. These metal cannulae are 13 to 16 inches long and are equipped with inflatable cuffs for securing the cannulae in place. The tips of the cannulae are curved and vary in outside diameter from 0.125 to 0.375 of an inch.

The coronary branches were perfused at a constant rate separately from individual Dale-Schuster pumps. Systemic arterial blood pressure and perfusion pressure were measured by electrical manometers (Lilly, Statham, and Sanborn), while heart rate and changes in electrocardiographic activity were determined by a Sanborn electrocardiograph. Respiration was recorded by means of a pneumograph and a Statham transducer. All recordings were continuously monitored in two polyviso recorders. Such perfusions were carried out on the following preparations: (a) one dog in which the right and left main coronary arteries were perfused separately; (b) two dogs in which the main branches of the left coronary artery (anterior descending and left circumflex) were perfused separately; (c) three dogs in which the left circumflex branch was perfused while injections were made into the left anterior descending branch by a catheter; and (d) two dogs in which the left anterior descending branch was perfused while injections were made into the left circumflex branch by a catheter. Embolization by lycopodium spores was accomplished in the usual manner in all coronary arteries, and changes in the behavior of the perfusion pressures, systemic arterial blood pressure, heart rate, cardiac electrical activity, and respiration were observed.

Results

EFFECTS OF EMBOLIZATION ON CORONARY
BLOOD FLOW AND CORONARY SINUS
VENOUS BLOOD OXYGEN SATURATION
IN NORMAL DOGS

Indirect Coronary Arterial Embolization
via Ascending Aorta

Embolization (by 0.05 and 0.1 ml. of 5 per cent lycopodium spore suspension) produced a sudden and marked decrease in coronary venous outflow which lasted less than a minute and was accompanied by a decrease in mean arterial blood pressure and usually by a slight increase in heart rate (fig. 1); in some experiments, however, heart rate was unchanged or decreased. In addition, respiration slowed or a momentary period of apnea occurred, followed by a prompt return to normal. The initial decrease in coronary blood flow was followed by a prolonged increase, beginning within the first minute of the decrease in flow, and persisting for approximately eight minutes. The maximal effect was usually reached within the second or third minute, but not later than the fifth minute, unless the dose was large (1.0 ml.). After reaching its peak, the increased flow usually returned to the control level within 10 minutes and did not fall below this. During the increase in coronary blood flow, coronary venous oxygen content and saturation were invariably increased. Mean arterial blood pressure fell slightly (fig. 1); in some experiments, however, heart rate was unchanged or decreased. In addition, respiration slowed or a momentary period of apnea occurred, followed by a prompt return to normal. The initial decrease in coronary blood flow was followed by a prolonged increase, beginning within the first minute of the decrease in flow, and persisting for approximately eight minutes. The maximal effect was usually reached within the second or third minute, but not later than the fifth minute, unless the dose was large (1.0 ml.). After reaching its peak, the increased flow usually returned to the control level within 10 minutes and did not fall below this. During the increase in coronary blood flow, coronary venous oxygen content and saturation were invariably increased. Mean arterial blood pressure fell slightly (fig. 1). The increased coronary blood flow and coronary venous oxygen content and saturation were associated with a narrowing of the coronary arteriovenous oxygen content and saturation and an apparent increase in cardiac oxygen metabolism. Arterial oxygen saturation was only slightly lowered in most experiments as a result of the slowing of respiration. The electrocardiogram changes consisted of elevation of the S-T segment and depression of the T wave, followed by peaking of the T wave. These changes were usually transitory during the first injection of small doses (0.05 to 0.1 ml.), but large doses (0.5 to 1.0 ml.) or repeated small doses produced permanent effects.

The effects showed considerable variability
Effects of a small dose (0.13 ml. of 1 per cent suspension) of lycopodium spores injected directly into the left coronary (circumflex, anterior descending) arterial branches. From top to bottom, the graph shows average values plotted for coronary venous oxygen saturation, coronary sinus blood flow, heart rate, and mean arterial blood pressure. Note the initial decrease in coronary blood flow accompanied by a fall in blood pressure immediately following embolization. Beginning within the first minute of the decrease in flow, there is an increase in flow and coronary venous oxygen saturation. At the same time, blood pressure continued to decrease slightly and then rise toward the control level.

in degree, but they were consistent in direction. It was generally observed that the larger the size of the dose of lycopodium, the greater were the responses. Attention was also given to the number of responses that could be expected in any one animal from a particular dose repeated successively, since this was important to study the block of the responses by various chemical and surgical procedures. We found less reproducibility exhibited following repeated large doses. This was especially evident with doses of 0.5 ml. and above. Doses of 1.0 ml. were found to yield only two responses which could be repeated, while 0.05 to 0.1 ml. doses produced at least three comparable responses.

Selective Coronary Arterial Embolization

Coronary arterial injections into the circumflex and anterior descending branches of the left coronary in doses varying from 0.05 ml. to 0.13 ml. of a 1 per cent lycopodium suspension produced an immediate marked decrease in coronary blood flow lasting less than a minute. This was accompanied by a slight decrease in mean arterial blood pressure and, in general, by no significant changes in heart rate. There was a slowing of respiration or a momentary apnea. Immediately following the initial decrease in coronary blood flow, there occurred an increase in flow and in coronary venous oxygen content and saturation, beginning within the first minute after the injection. This increase in coronary blood flow persisted for approximately eight minutes. The maximum flow occurred by the second or third minute, but not later than the fifth minute. It returned to the control level usually by the tenth minute. During the increase in coronary blood flow, mean arterial blood pressure and heart rate changed only slightly (fig. 2). Arterial oxygen saturation decreased slightly, while the arteriovenous oxygen difference narrowed and cardiac oxygen metabolism apparently increased. The electrocardiographic changes were the same as those reported above.

If larger doses were employed and the animal did not survive the emboli, there followed a continuous decrease in coronary blood flow, mean arterial blood pressure, and heart rate. The same relationship of dose to response and reproducibility was obtained following direct coronary arterial embolization, as was observed in the experiments during indirect coronary embolization.

Autonomic Blocking Agents

To investigate the importance of reflex mechanisms to the initial decrease and de-
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TABLE 1

<table>
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<tr>
<th>Procedure</th>
<th>Experiment number</th>
<th>Dose (ml.)</th>
<th>Injection sequence*</th>
<th>Coronary sinus flow (ml./min.)</th>
<th>Mean arterial blood pressure (mm./Hg)</th>
<th>Control blood pressure</th>
<th>Decreased flow</th>
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*Injection sequence indicates the number of previous embolizations given to animals.
†Closed-chest preparation.
‡Open-chest preparation.
§With splanchnic division.
||Norepinephrine continuous infusion.

layed increase in flow and coronary venous oxygen saturation, intravenous and coronary arterial injections of autonomic blocking agents (hydralazine, 1.0 to 10 mg./Kg.; hexamethonium, 1.0 to 10.0 mg./Kg.; atropine, 0.1 to 1.0 mg./Kg.; dibozane, 0.5 to 1.0 mg./Kg.; and epidural procaine, 10 to 20 ml. of a 2 per cent solution) were administered. None of these had any significant influence on the responses to coronary embolization.

EFFECTS OF CORONARY EMBOLIZATION ON CORONARY BLOOD FLOW FOLLOWING CARDIAC DENERVATION AND ADRENALECTOMY

To determine if a centrally mediated neural reflex was responsible for the responses obtained by coronary embolization, interruptions of appropriate nervous pathways were produced. The results are summarized in table 1.

Bilateral Thoracic Sympathectomy

Two animals were successfully prepared, on which four embolizing determinations were made. Interruption of the sympathetic innervation did not block the response, which was qualitatively comparable to that observed in normal dogs (fig. 1).

Bilateral Vagotomy

Three animals were prepared, two of which had had bilateral sympathectomy from the stellate ganglia through T9 just prior to cannulation of the coronary sinus; in these, the heart was completely denervated. Neither complete cardiac denervation nor bilateral vagotomy alone abolished the response.

Bilateral Lumbar Sympathectomy and Splanchnic Division

This procedure produced such systemic circulatory instability that a continuous norepinephrine infusion was necessary to maintain an adequate blood pressure in the single animal reported. These procedures did not block the response.

Bilateral Adrenalectomy

This was carried out in two reported prep-
FIGURE 3
Coronary dilatation by embolization with lycopodium spores. Catheter in the first portion of the left anterior descending branch. The volume of radiopaque material (2 ml.) injected was the same in all cases. All pictures were obtained in the same dog. (A) Control angiogram (blood pressure, 180/138; heart rate, 83) before lycopodium spores (0.1 ml. of 1 per cent) injected into left anterior descending branch; B (blood pressure, 170/130; heart rate, 100) and C (blood pressure, 163/130; heart rate, 120) are the response angiograms taken at 15-second and 3-minute intervals, respectively, following the lycopodium injection. The control angiogram (A) demonstrates, in addition to the distribution of the left anterior descending branch, a reflux of the contrast medium into the circumflex branch. Note in B the marked degree of obstruction in the left anterior descending branch with as much, if not more, reflux into the left circumflex.
FIGURE 4

Effect of obstruction (by embolization of a coronary arterial branch) producing redistribution and reflex of the contrast medium into nonembolized coronary arterial branches. Catheter in the first portion of the left anterior descending branch just distal to proximal branches of this vessel. The volume of radiopaque material (2 ml.) injected was the same in both cases. Both pictures were obtained in the same dog, with the control and response angiograms taken 15 seconds apart. (A) Control angiogram (blood pressure, 175/135; heart rate, 90); (B) (blood pressure, 160/136; heart rate, 105) after lycopodium spores (0.1 ml. of 1 per cent) injected into left anterior descending branch. Note in B the marked degree of obstruction in the main left anterior descending coronary artery. At the same time, there is an increased distribution of the radiopaque material into a large branch, as well as other smaller branches coming off the main trunk (left anterior descending), just proximal to the tip of the catheter. All of these branches were less well outlined in the control (A). In addition, there is reflex of the contrast medium into the left circumflex branch. The increased filling of these branches, as well as the reflex into the circumflex branch, is all due to the block produced by the lycopodium in the distribution of the main left anterior descending branch with redistribution of the dye into these nonembolized branches. The animal survived the injection.

Spinal Cord Transection

Two animals successfully withstood C6 to C7 cord division. This produced such profound circulatory and respiratory instability that the coronary blood flow response to embolization, though definitely present, was much reduced in magnitude.

SELECTIVE ARTERIOGRAPHY AND CONTROLLED PERFUSION OF THE CORONARY ARTERIAL BED IN CORONARY EMBOLIZED DOGS

By these means, we hoped that the degree of mechanical block and/or vasospasm responsible for the effect could be ascertained. In as seen in the control (A), making the occurrence of reflex vasoconstriction in the latter bed unlikely. The angiogram (C), taken three minutes following embolization, shows that coronary dilatation occurs as evidenced by an increase in the size and number of visible coronary vessels. Animal recovered from injection.
addition, we intended to determine to what extent the increase in flow observed following the decrease was due to vasodilatation, intercoronary anastomosis, or coronary arteriovenous shunts.

**Angiographic Demonstration of Selective Arterial Embolization by Lycopodium Spores**

Selective coronary angiograms were made of the main left coronary arteries alone (anterior descending, circumflex) in 24 dogs, and in combination in 10 dogs following embolization by lycopodium spores. In all cases, the effects were essentially the same.

**Single Catheterization of Individual Coronary Arteries.** Angiograms made following injection of lycopodium spores (0.1 ml of 1 per cent) into either of the two main branches (anterior descending, circumflex) of the left coronary artery showed extinction of the distal parts of the vessel embolized (fig. 3). At the same time, reflux of contrast medium occurred in the nonembolized vessels in most experiments, especially in the left circumflex when the left anterior descending was embolized. The initial effect was followed by vasodilatation and a gradual return to a normal pattern (fig. 3). During embolization, blood pressure decreased slightly, and heart rate generally increased slightly, but in some experiments, it either remained the same, or decreased slightly. The electrocardiographic (V3 or V4) changes recorded directly over the area embolized were consistent with those previously seen, viz., a depression of the T wave, S-T elevation followed by peaking of the T wave. With repeated embolization, there occurred disturbances in rhythm leading to sudden death by ventricular fibrillation, or more often to complete A-V block terminating in cardiac standstill followed later by ventricular fibrillation. The marked vasodilatation is demonstrated by the increase in size of the well-defined vessels, previously visible, and by the increased definition of other vessels. In addition, the appearance of small vessels where none was previously visible, and of a haze around the coronary bed due to an increase in the amount of contrast substance in the finer vessels of the myocardial tissue, may also reflect dilatation and/or intercoronary anastomotic channels, as well as different types of arterial shunts previously mentioned. The initial effect of embolization is apparently caused by mechanical block of the fine coronary vessels.

Five dogs out of the 24 which were studied by single catheterization were selected for

**FIGURE 5**

Effect of embolization (by lycopodium spores) on coronary artery. Combined catheterization of the main branches of the left coronary. Catheters in the first portion of the left anterior descending and circumflex. The volume of radiopaque material (3 ml.) injected was the same in each case. All pictures were made in the same dog. A (dye injection in left circumflex branch, blood pressure, 145/103; heart rate, 200) and B (dye injection in left anterior descending branch, blood pressure, 130/100; heart rate, 210) are control angiograms before lycopodium spores. (0.1 ml. of 1 per cent) injected into left anterior descending branch. C (dye injection in left anterior descending branch, blood pressure, 140/103; heart rate, 210), D (dye injection in left circumflex branch, blood pressure, 145/98; heart rate, 220), and E (dye injection in left anterior descending branch, blood pressure, 125/95; heart rate, 210) are the response angiograms taken at 15-, 20-, and 30-second intervals, respectively, following the lycopodium injection. Note marked degree of obstruction in the left anterior descending branch pictured in C and E. No reflex constriction occurred in left circumflex branch (D), during continued marked degree of obstruction of the left anterior descending branch (C and E), compared with A, control. Furthermore, there is reflux of contrast medium into left circumflex in C and E at a time when left anterior descending is obstructed, which is also against the occurrence of reflex vasospasm in the circumflex branch. Also note the delayed run off of the contrast medium in the left anterior descending still seen in picture D following injection made in C. This is not reflux since a blank (film taken without injection of contrast medium) shot between C and D demonstrated contrast medium in left anterior descending. There is gradual relief of the obstruction as witnessed by the gradual reappearance of vessels. Animal recovered from injection.
FIGURE 6
Demonstration of constriction (by pitressin) and obstruction (by lycopodium) with combined catheterization and simultaneous injections into left coronary arterial branches. Catheters in the first portion of the left anterior descending and circumflex. The volume of radiopaque material (3 ml.) injected was the same in each case, and the contrast medium was injected simultaneously into both catheters. All photographs were taken in the same dog with the control and response angiograms taken 15 seconds apart. (A) Control angiogram (blood pressure, 138/113; heart rate, 120); (B) (blood pressure, 125/112; heart rate, 130) after pitressin (0.03 unit/Kg.) injected into left anterior descending branch. (C) Control (blood pressure, 158/113; heart rate, 120); (D) (blood pressure, 150/110; heart rate, 140) after lycopodium spores (0.1 ml. of 1 per cent) injected into left anterior descending branch. In B, there is marked constriction of
special studies on the occurrence of reflex angiospasm by utilizing anatomical distribution of certain arterial branches of the left coronary artery (anterior descending, circumflex). In these animals, numerous branches were observed to come off the proximal parts of these vessels. During catheterization, the catheter was placed slightly distal to these branches, so that they would be poorly outlined in the control angiogram by the contrast medium, and injection of emboli would not enter them directly. Following embolization, the contrast medium was again injected into the catheter to determine if more would concentrate in these branches due to redistribution (reflux) of the opaque substance, in addition to the appearance (reflux) of the contrast medium in the opposite main branch. In these cases, there occurred a redistribution of the contrast medium into all these adjacent branches, which indicated the absence of reflex spasm, not only in the opposite nonembolized main branch (left anterior descending, left circumflex), but also in the nonembolized branches of the same vessel embolized (fig. 4).

Combined Catheterization of Individual Coronary Arteries. By combined catheterization of the left coronary arterial bed (anterior descending and circumflex), a comparison was made of the pattern of the nonembolized with the embolized portions. The angiograms of the embolized branches in these experiments showed the same characteristic pattern as that demonstrated in the single catheterization experiments; however, the angiograms of the nonembolized vessels taken during the initial effects of embolization did not change from the control pattern, which again demonstrated the absence of reflex vasospasm in these vessels. Less than a minute later there was dilatation of the bed.

We also found that repeated (approximately three or more injections) embolization (0.1 ml. of 1 per cent suspension) produced a lasting embolized angiographic pattern up to the time of death of the animal; i.e., the contrast medium remained in the vessel because of a markedly delayed run-off of the radiopaque medium caused by the mechanical block. The results were the same whether the contrast medium was injected into the branches separately (fig. 5) or simultaneously following embolization (fig. 6). This eliminates the effect of the contrast medium as a cause for interfering with the possible occurrence of reflex vasoconstriction on the basis of its slight vasodilator action.\textsuperscript{19,20}

Effects of Autonomic Blocking Agents on Embolization. Blocking drugs, viz., atropine, TEA, and hexamethonium, were tested in 8 of the 34 animals, since other experiments suggested that atropine, vagotomy, and sympathectomy counteracted the reflex spasm believed to accompany occlusion of a coronary artery.\textsuperscript{1,6,21,22} These autonomic blocking agents did not alter the angiographic pattern following embolization.

Effects of Coronary Vasodilator Drugs on Embolization. In view of the belief that coronary vasodilators are effective because of preventing or minimizing coronary spasm following experimental coronary occlusion, the vasodilator drugs, nitroglycerin and sodium cyanide, were studied on embolization in 7 of the 34 animals. There were no marked changes in the pattern of embolization, although a slightly less marked effect occurred in two experiments.

Comparison of Coronary Obstruction by Embolizing Agents and Constriction by Pitressin. Since previous studies have shown that intra coronary injections of pitressin produce severe constriction of the coronary ves-
Effect of acute obstruction of the left anterior descending coronary arterial branch by a special occluding catheter. The volume of radiopaque material (2 ml.) injected was the same in all cases. All photographs were obtained from the same dog. (A) Control angiogram (blood pressure, 180/150; heart rate, 110) before occlusion by the catheter (tip of catheter in the left anterior descending artery and occluding end of catheter just
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sels that can be demonstrated by angiography, a comparison of this pattern with that of embolization was made in 8 animals of the 34 studied. Experiments to elicit vaso-
spasm of adjacent coronary arteries during direct constriction of one main coronary ar-
tery by pitressin were attempted. The ex-
periments with pitressin showed that direct constriction of one coronary artery by
pitressin did not lead to reflex vasospasm in
the opposite bed (fig. 6).

Coronary Obstruction by a Special
Occluding Catheter
To simulate more closely the occurrence of occlusion of a major coronary artery brought about by acute ligation (experimentally), or by a sudden marked degree of narrowing (clinically), a special occluding catheter was designed that would obstruct a single main coronary arterial branch without occluding flow into the others. In this way, acute occlusion was produced with chest intact, and angiograms were immediately taken of the occluded vessel. Five dogs were subjected to this method of occlusion of one major left coronary artery branch (anterior descending or circumflex), and in no instance did the angiograms of the occluded vessel show spasm (fig. 7); instead, coronary vasodilatation was evident in the presence of increase in size of the visible vessels and by the occurrence of other vessels not previously seen.

Combined Cannulation and Perfusion of the Coronary Arteries
The embolizing agent, lycopodium spores, produced the usual characteristic response in the distribution of the coronary arterial branch injected, as evidenced by the same alteration in the electrocardiographic pattern, heart rate, and systemic arterial blood pressure, as well as an initial increase in perfusion pressure of the embolized coronary bed. Embolization failed to elicit an unequivocal inter-
coronary reflex spasm in the simultaneously perfused branch of the opposite bed. In general, the perfusion pressure of the nonembo-
lized bed decreased slightly (indicative of an increase in flow) at the time when perfusion pressure in the embolized bed had increased.

Discussion
Possibly the most important aspect of these experiments is that embolization of the cor-
onary circulation produces a prolonged in-
crease in coronary blood flow after the expected initial temporary decrease. Since the increase in coronary blood flow was ac-
companied by a rise in coronary venous oxygen saturation, it is most probable that some portion of the myocardium experienced an elevation of oxygen level. Questions raised by this and other corollary studies include whether true spasm of coronary vessels, which is suspected in clinical coronary occlusion, accompanies the mechanical embolization (mechanical block), whether the primary fac-
tor in the secondary dilatation is chemical or reflex, and whether the rise in coronary ve-
nous pO\textsubscript{2} represents a true change in tissue oxygenation or a shunting mechanism with no increase in pO\textsubscript{2} of the tissue involved. The fact that these responses were not abolished by autonomic blocking agents or by complete cardiac denervation and adrenaleetomy would suggest the possibility of a local block by the emboli as being responsible for the initial marked decrease in flow, and an intrinsic or extrinsic local mechanism being entirely re-
sponsible for the dilatation and increase flow provided coronary arteriovenous shunts are not participating.

The exact location of the mechanical block

\begin{figure}
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\includegraphics[width=\textwidth]{coronary_reflexes.png}
\caption{Coronary reflexes.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{coronary_obstruction.png}
\caption{Coronary obstruction by a special occluding catheter.}
\end{figure}

\begin{figure}
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\includegraphics[width=\textwidth]{combined_cannulation_perfusion.png}
\caption{Combined cannulation and perfusion of the coronary arteries.}
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\caption{Discussion.}
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\begin{figure}
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\includegraphics[width=\textwidth]{specific_factors.png}
\caption{Specific factors affecting coronary reflexes.}
\end{figure}

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above coronary ostia in ascending aorta. B (blood pressure, 200/158; heart rate, 125) and C (blood pressure, 200/158; heart rate, 110) are response angiograms taken at 3- and 5-minute intervals, respectively, following advancement of the special catheter to the point of obstruction of the left anterior descending branch alone (circum-
flex, not occluded). Note that in B there is no reflex spasm of the occluded branch (left anterior descending). The angiogram (C) taken during two minutes of occlusion shows that coronary dilatation occurs, as evidenced by an increase in the size of visible coronary vessels and a lighter appearance (haze) of the heart probably due to an increase in the amount of contrast substance in the finer vessels and capillaries of the myocardial tissue. Ventricles fibrillated while catheter was being withdrawn from the vessel.

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by the lycopodium spores was not determined in these studies. The diameter of the spores is between 20 and 40 μ; however, the size of vessels obstructed, the areas of the heart involved (as determined by areas of distribution of the coronaries both embolized and nonembolized, examined histologically) as well as depth of involvement of the heart tissue (epicardial, myocardial and endocardial), and the histological changes produced could not be ascertained, since histological examination of these hearts had to be deferred for later studies. However, Hamburger, Priest, and Bettman showed that spores were found in the arterioles and capillaries. Most recently, studies by Agress and associates and have described the location of larger emboli (plastic microspheres) used to produce infarction, while Bing and associates have described their location as well as the early and late histological changes in the hearts following embolization.

The finding of increased coronary flow is in agreement with the findings of Eckenhoff and associates and Gregg and with the recent investigations made following occlusion of cannulated left circumflex coronary arteries in dogs by Coffman and Gregg. In addition, our experiments are in agreement with the findings by Sayen and associates, who demonstrated an increase in myocardial oxygen availability following temporary occlusion and release of small coronary arterial branches. Coronary dilatation is one mechanism which occurs during this increase in flow, but this may not be the complete picture. Whether anastomotic channels of various types (arterio-arterial, arteriovenous, arterioluminal, arterial-sinusoidal, and Thebesian veins) are also in part responsible, is not known. However, the existence of these would help to explain the transitory block by the emboli following limited number of injections. Prinzmetal and associates have shown by perfusing human hearts post mortem, and by the injection of glass spheres of known sizes through one of the coronary arteries, that the spheres could be collected at the opposite coronary artery, the coronary sinus, and the ventricular cavities.

On the basis of the angiograms, there is no evidence for spasm in the obstructed or nonobstructed coronary arteries investigated in this study. The evidence against the initial effect of embolization being the result of coronary arterial spasm of the obstructed vessel, and intercoronary reflex spasm of adjacent nonembolized coronary vessels, is as follows: (a) the occurrence of reflux of contrast medium into nonembolized coronary arterial branches of the branch embolized as well as into the adjacent coronary bed; (b) the presence of a normal coronary angiogram of the adjacent bed at a time when the embolized coronary artery demonstrates the characteristic initial embolized pattern; (c) the presence of a normal nonconstricted angiographic pattern in the adjacent bed at the time that marked constriction from pitressin occurred in the opposite bed; (d) the negative suggestive evidence as demonstrated by the autonomic blocking agents, atropine, tetraethylammonium chloride, and hexamethonium (being ineffective in blocking the response); (e) the negative suggestive evidence by the vasodilator agents, nitroglycerin and sodium cyanide, in not markedly altering the response; (f) the presence of a normal coronary angiogram in the presence of occlusion of the coronary vessel by a special coronary occluding catheter. In addition, preliminary findings on combined cannulation and perfusion of the coronary arteries during embolization of individual branches support our angiographic evidence concerning spasm by adding flow studies, and for the nonexistence of intercoronary reflex spasm, since a decrease in coronary vascular resistance occurred in the nonembolized perfused vessel rather than an increase, suggestive of vasodilatation. The latter finding is in agreement with the observations made by others.

The initial effect of embolization by lycopodium spores is therefore the result of mechanical block by the emboli of small coronary vessels, through which flow is impeded. This pattern is of a transitory nature provided the injections are not repeated excessively, or of a large dose, which then results in a lasting embolized pattern.
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In conclusion, from the results of these studies, it is difficult to account for spasm in the obstructed vessel, and intercoronary reflex spasm of the adjacent vessels as being precipitating factors in cardiogenic shock; therefore, one must look elsewhere for additional factors which may be involved in order to explain the many complex problems associated with this condition.

Nevertheless, the basic disturbance in cardiogenic shock resulting from severe myocardial ischemia is still the result of a diminution in cardiac output, as has been regularly demonstrated both in humans and experimental animals.10, 11, 24, 31-35 Recently, Bing and associates24 have investigated the circulatory, pathological, and biochemical aspects of this problem, and have shown that embolization of the coronary arteries by spheres, in addition to producing a significant fall in cardiac output, coronary blood flow, and myocardial oxygen consumption also resulted in a significant reduction in the utilization of glucose, pyruvate, and lactate by the heart, as well as significant alterations in various enzyme systems. However, the many problems involved in this mosaic syndrome are still far from being completely answered.

Summary

The cardiovascular effects of selective coronary embolization were studied with improved techniques in an attempt to obtain evidence for the existence of intercoronary reflexes and their role in potentiating myocardial ischemia.

These studies demonstrated that embolization of the coronary arterial bed by lycopodium spores produced an initial marked decrease in coronary blood flow followed by a maintained (approximately 10 minutes) increase which was accompanied by an increase in coronary sinus venous oxygen saturation. Supporting evidence was obtained from selective coronary angiograms and from changes in coronary vascular resistance. Attempts at eliminating these responses by certain autonomic blocking agents (atropine, hydralazine, tetraethylammonium chloride, hexamethonium, and dibozane), surgical denervation of the heart, and adrenalectomy were all ineffective. Experimental evidence obtained by comparing the initial effect of embolization with pitressin vasoconstriction and coronary occlusion all led to the conclusion that reflex coronary spasm does not occur during coronary occlusion. The cause of the initial decrease in coronary blood flow during embolization (lycopodium spores) is, therefore, mechanical block within the distribution of the vessel by the emboli.

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References

7. MEILMAN, E., AND KRATER, O.: Clinical studies on veratrum alkaloids: I. Action of proto-

Effects of Selective Coronary Embolization on Coronary Blood Flow and Coronary Sinus Venous Blood Oxygen Saturation in Dogs
James W. West, Tachio Kobayashi and Fred S. Anderson

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