Evaluation of Procedures Designed to Enhance Coronary Collateral Blood Flow

By Robert M. Berne, M.D., Richard D. Jones, B.A., and Frederick S. Cross, M.D., Ph.D.

The high incidence of coronary artery disease in man has prompted extensive research efforts in the direction of improving blood flow to the heart muscle. Attempts to achieve this goal have taken many forms and may be summarized as follows: (1) scarifying procedures designed to encourage the growth of new vascular channels into the heart from extracardiac sources; (2) retrograde perfusion of the myocardium via the coronary sinus; (3) direct surgical removal of the obstructing lesion in the coronary vessels with or without replacement of a segment of coronary arteries; (4) myocardial implantation of a large extracardiac artery; (5) ligation of an internal mammary artery; (6) combinations of one or more of the above procedures.

Since (a) retrograde perfusion via the coronary sinus is only of temporary value, (b) internal mammary artery ligation does not divert blood to the myocardium, and (c) surgical removal of coronary thrombi and replacement of diseased vessel segments are still extremely difficult and hazardous, procedures involving the production of vascular adhesions between the heart and other tissues, or arterial implantations into the myocardium are currently in favor. Practically all of the methods described appear to increase the collateral circulation of the heart of the normal experimental animal. Whether they are equally effective in the arteriosclerotic heart remains to be demonstrated. In humans with coronary artery disease objective improvement is difficult to assess. In the experimental animal it is not known whether the procedures employed would increase coronary collateral circulation under conditions mimicking arteriosclerotic heart disease in man, as emphasized by Gregg. Coronary narrowing alone is probably the strongest stimulation to the development of cardiac collateral blood flow, and it is therefore necessary to demonstrate that the surgical procedures mentioned above will increase the collateral circulation over and above that produced by coronary artery narrowing alone. The purpose of the present study is to evaluate some of the existing methods for inducing the development of cardiac collateral vessels under conditions simulating, in some respects, occlusive coronary artery disease in man.

Methods

Experiments were performed under pentobarbital (30 mg./Kg.), on mongrel dogs ranging in weight from 12 to 26 Kg., employing aseptic technique. A thoracotomy was made in the fourth left intercostal space. Under electrocardiographic control the circumflex branch of the left coronary artery was ligated with silk over a probe from 0.9 to 1.2 mm. in diameter within 0.5 cm. of its origin. The ligature was removed and reapplied over a larger probe in animals in which the T-wave and S-T-segment changes did not return to normal, or nearly normal, upon removal of the probe. The chest was closed in layers, the air removed from the intrapleural space, and the dogs given penicillin for four days postoperatively.

Three procedures reported to improve the coronary collateral circulation were carried out in one series of dogs at the time of left circumflex artery narrowing and in another series of animals six weeks after coronary constriction. The procedures were: (1) placement of 0.25 to 0.5 Gm. of sterile shredded asbestos over the surface of the heart; (2) suturing of the mediastinal fat pad to the abraded left lateral surface of the heart in conjunction with the application of asbestos; (3) implantation of the internal mammary artery into...
coronary collateral blood flow

the left ventricular wall in conjunction with application of Ivalon sponge to the denuded surface of the left ventricle.

Procedures 1 and 3 were done essentially as described by Beck and Vineberg, respectively. The pericardial fat pad was developed in procedure 2 by dissecting it free from the surface of the pericardium, retaining the blood supply by way of the pericardiophrenic vessels. The underlying pericardium was then opened, the epicardial surface of the heart abraded, and the fat pad lightly sutured over as wide an area of the left ventricle as possible.

Twelve weeks after the left circumflex coronary artery was narrowed, coronary pressure and flow studies were performed. The circumflex branch of the left coronary artery was dissected free from the fibrous tissue just distal to the point of constriction, and after the administration of heparin, was cannulated in both directions (fig. 1). Mean arterial pressure was adjusted to 100 mm. Hg by the judicious bleeding from or infusion of blood into a jugular vein and/or the use of an adjustable clamp on the lower thoracic aorta. All flow and coronary pressure measurements were made at an arterial pressure of 100 mm. Hg. Blood from a cannulated carotid artery flowed through a rotameter, for flow measurement, and into the distal segment of the circumflex artery (fig. 1). The carotid artery cannula was of sufficient diameter to offer no significant resistance to blood flow.

Retrograde flow measurement, although not an accurate measure of blood flow to the ischemic area, served as an index of the extent of the interarterial collateral circulation. For such measurement, hemostat 3 (fig. 1), between the rotameter and Y tube, was closed, and the screw clamp marked “retro flow” was opened. The magnitude of flow through the constriction against no resistance served as an index of the degree of narrowing that had been produced. For such determinations the screw clamp marked “flow thru constriction” was opened. Retrograde flow from the distal left circumflex artery and blood flow through the constricted segment of this vessel were measured in graduated cylinders for 30-second intervals against atmospheric pressure at the level of the point of coronary cannulations. The values obtained represent the average of four to eight separate determinations. The manometer on the left (fig. 1) recorded aortic pressure. The manometer on the right (fig. 1) recorded circumflex coronary artery pressure during perfusion of the distal coronary artery via the proximal segment of the same vessel. This served as an additional index of the degree of narrowing produced. Electrocardiograms (AVR) were taken before, during, and after each measurement of PCP or retrograde flow.

At the conclusion of each experiment the myocardium supplied by the left circumflex coronary artery was stained with diluted India ink, and a barium gelatin mixture at 40 C. was infused into the distal cannula at a pressure of 200 mm. Hg until either flow ceased or the mixture poured forth from other vessels into the warm bath in which the heart was suspended. After cooling overnight, the heart was dissected by the Schlesinger technique, x-rayed, and the stained and unstained portions of the myocardium separated and weighed. Flows are expressed as ml./min./100 Gm. of stained heart. The degree of constriction was checked with suitable probes, and the patency of the proximal coronary artery and the implanted internal mammary artery was determined.

The experimental animals have been divided into the following groups: (1) normal unoperated animals, 2 dogs; (2) controls with circumflex artery narrowing, 9 dogs; (3) controls in which a sham thoracotomy was performed six weeks after left circumflex narrowing, 8 dogs; (4) animals treated with asbestos at the time of circumflex narrowing, 9 dogs; (5) animals treated with asbestos six weeks after circumflex narrowing, 8 dogs; (6) animals treated with abrasion of the

Circulation Research, Volume X, February 1968
cardiac surface and application of the mediastinal fat pad and asbestos at the time of circumflex narrowing, 10 dogs; (7) animals treated with abrasion of the cardiac surface and application of the mediastinal fat pad and asbestos six weeks after circumflex narrowing, 12 dogs; (8) animals treated with internal mammary artery implantation, abrasion of the cardiac surface, and application of an Ivalon sponge to the myocardium at the time of circumflex narrowing, 12 dogs; (9) animals treated with internal mammary artery implantation, abrasion of the cardiac surface, and application of an Ivalon sponge to the myocardium six weeks after circumflex narrowing, 10 dogs. Thirteen dogs were eliminated from the series: six because of technical difficulties at the time of pressure and flow studies, six because of gross myocardial infarcts, and one because of severe cardiac tamponade. In the dogs with myocardial infaracts, the circumflex artery narrowing was so severe that the vessel became completely occluded before there was an opportunity for collateral vessels to develop.

Results

In figure 2, retrograde coronary flow is plotted as a function of flow through the constricted segments of the coronary vessels for all the experiments. It is apparent that with more marked narrowing of the left circumflex artery, as evidenced by the low flows through the constricted segment, there is a greater retrograde flow. A procedure which enhances the development of collateral vessels over and above that produced by narrowing alone would yield greater retrograde flows at any given degree of constriction. However, it is evident from figure 2 that the different groups of treated dogs (groups 4 through 9) cannot be distinguished from the control dogs (groups 1 through 3) or from each other.

The peripheral coronary pressure (PCP) is also indicative of the degree of collateral development. Figure 3 is a plot of PCP against flow through the constricted coronary segment. Here, too, no difference can be observed between control dogs and dogs subjected to various "revascularizing" procedures. Further indication that the changes in retrograde flow and PCP were similar in all the experimental groups can be seen in table 1. Retrograde flow, PCP, and the average pressure drop (10 to 17 mm. Hg) across the constricted segments of the left circumflex arteries in groups 2 through 9 were all of the same magnitude. Postmortem measurements of the constriction with calibrated probes essentially corroborated estimates of diameter of the constricted segments based upon flow through, and pressure drops across, the constricted segments.

Except in dogs with myocardial infaracts which were eliminated from the series, elec-
trocardiograms taken during perfusion of the left circumflex coronary artery were essentially normal. During measurement of PCP, slight to moderate T-wave inversions occurred, and these changes became much more marked during retrograde flow determinations. No distinction based upon electrocardiographic changes could be made between the different groups of animals.

In twenty experiments in groups 2, 4, 7, 8, and 9, occlusion of the left anterior descending artery during measurements of retrograde flow produced about a 50 per cent reduction in retrograde flow. Average flow reduction in the different groups fell between 45 and 53 per cent. The true contribution of left anterior descending flow to left circumflex retrograde flow and to the muscle supplied by the left circumflex coronary artery may be greater than 50 per cent, since competition for common channels between anterior descending flow and flow via other collaterals is eliminated during the measurement.

Twelve of the 22 dogs with internal mammary artery implants were found to have the implanted arteries thrombosed at autopsy. However, of the last 10 dogs subjected to the procedure, only 2 showed thrombosis of the implant, strongly suggesting that surgical technique is important in obtaining patent vessel implants.

In five dogs, the effect of clamping of the implanted vessel on retrograde flow was studied. Two of these dogs showed a reduction in retrograde flow when the implanted vessel was clamped. In one dog, retrograde flow decreased from 82 to 60 ml./min./100 Gm. of muscle and in the other dog from 62 to 57 ml./min./100 Gm. of muscle. In each of these experiments, these values represent the averages of five to six determinations.

X-rays of the unrolled, injected hearts revealed the existence of moderate to extensive collateral vessels in all hearts in which constriction of the circumflex coronary artery resulted in increased retrograde flow and PCP. No differences could be detected in the extent of intercoronary collateral vessels between hearts of sham-operated dogs six weeks after circumflex narrowing, and those subjected to any of the revascularizing procedures. Only one of 17 dogs treated with asbestos showed the presence of barium in the fibrous tissue found adherent to the surface of the heart at postmortem, and only 2 of 22 dogs treated with the application of the mediastinal fat pad had barium in the fat pad following injection. In the group of dogs subjected to internal mammary artery implantation, 8 of the 10 animals with patent internal mammary arteries at postmortem showed barium in this vessel and in the con-
TABLE 1

Average Values for Retrograde Flow, Peripheral Coronary Pressure, and Pressure Drop Across Constricted Coronary Vessels in Different Experimental Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Retrograde flow ml/min./100 Gm.</th>
<th>PCP mm. Hg</th>
<th>Pressure drop across constriction</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>13</td>
<td>0*</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>56</td>
<td>52</td>
<td>15</td>
<td>Circumflex narrowing.</td>
</tr>
<tr>
<td>3</td>
<td>59</td>
<td>62</td>
<td>11</td>
<td>Circumflex narrowing and sham thoracotomy.</td>
</tr>
<tr>
<td>4</td>
<td>59</td>
<td>62</td>
<td>17</td>
<td>Asbestos at time of narrowing.</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>62</td>
<td>10</td>
<td>Asbestos six weeks post narrowing.</td>
</tr>
<tr>
<td>6</td>
<td>44</td>
<td>40</td>
<td>11</td>
<td>Fat pad at time of narrowing.</td>
</tr>
<tr>
<td>7</td>
<td>58</td>
<td>50</td>
<td>16</td>
<td>Fat pad six weeks post narrowing.</td>
</tr>
<tr>
<td>8</td>
<td>44</td>
<td>53</td>
<td>11</td>
<td>Artery implant at time of narrowing.</td>
</tr>
<tr>
<td>9</td>
<td>54</td>
<td>58</td>
<td>14</td>
<td>Artery implant six weeks post narrowing.</td>
</tr>
</tbody>
</table>

*No narrowing and unmeasurable pressure drop.

Discussion

In all previous studies in which different myocardial revascularizing procedures were evaluated, the procedure was either carried out prior to, at the time of, or within a few days of the coronary narrowing. Such studies may test the prophylactic value of the procedures but can give no indication of their worth in the heart with atherosclerotic vessels. Furthermore, most of these earlier investigations relied solely upon per cent survivals or postmortem coronary injections to demonstrate their effectiveness and did not include flow or pressure measurements in the collateral vessels.

When several "revascularizing methods" were tested in hearts with previously narrowed left circumflex coronary arteries, no increase in the extent of coronary collateral circulation over and above that produced by narrowing alone was observed. Asbestos induced a powerful fibrotic reaction with the production of a dense avascular fibrous mass adherent to the heart and adjacent structures. Application of the mediastinal fat pad to the denuded epicardial surface did not result in the establishment of demonstrable vascular communications between the heart and the vascular fat pad. However, some measure of success was observed in the development of vascular connection between cardiac and extracardiac vessels by the implantation of the internal mammary artery into the left ventricular wall according to the method of Vineberg.6 Evidence for such communications was obtained principally from injection studies but was substantiated by the observation that a small decrease in circumflex artery retrograde flow occurred upon clamping of the internal mammary artery in two of five experiments.

These observations and the failure to find a difference in retrograde flow and PCP between control dogs and those subjected to the Vineberg procedure indicate that only a small amount of blood reached the myocardium via extracardiac channels. It should be emphasized, however, that in the present series of experiments only one of the major coronary arteries was narrowed, and the opportunity for intercoronary collateral vessels to develop was probably optimal. In arteriosclerotic heart disease Baroldi, Mantero, and
Seomazzoni have shown that the greatest collateral artery development occurred when one vessel was narrowed and the others were relatively normal. These authors also noted that, when two main coronary arteries were narrowed, intercoronary communications were fewer, and the areas supplied by the diseased arteries showed poor vascularization. Tissue hypoxia existed in these areas as a stimulus to collateral vessel growth, but inadequate blood supply was available. In the event that extracardiac vessels were implanted in such an area, it appears likely, from the present study, that the added stimulus of a pressure gradient to collateral vessel growth would encourage the formation of new channels between the implanted and local vessels. Furthermore, the absence of competing vascular channels from adjacent coronary arteries would in all likelihood lead to more extensive communications between the implanted and myocardial vessels than was found in the experiments described in this report.

A more rigorous test of the effectiveness of myocardial implantation of extracardiac arteries in revascularizing ischemic heart muscle could be performed in hearts in which both main coronary arteries had been previously gradually narrowed to a point where cardiac function became impaired. An experiment of this type would more closely simulate extensive coronary atherosclerosis in man, where intercoronary collaterals are poorly developed and, if present, are of relatively little value.

Summary

Three procedures reported to improve the coronary collateral circulation were carried out in dogs: (1) placement of 0.25 to 0.5 Gm. of sterile shredded asbestos over the surface of the heart; (2) suturing of the mediastinal fat pad to the abraded left lateral surface of the heart in conjunction with the application of asbestos; (3) implantation of the internal mammary artery into the left ventricular wall in conjunction with application of Ivalon sponge to the denuded surface of the left ventricle.

The effectiveness of these measures was determined in dogs with previously narrowed left circumflex coronary arteries. As judged by retrograde flows and peripheral coronary pressures, the collateral vessel development was not increased over and above that produced by narrowing alone. Coronary artery injection studies revealed that only internal mammary artery implantation produced vascular connections between cardiac and extracardiac vessels.

References

Evaluation of Procedures Designed to Enhance Coronary Collateral Blood Flow
Robert M. Berne, Richard D. Jones and Frederick S. Cross

_Circ Res._ 1962;10:142-147
doi: 10.1161/01.RES.10.2.142

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1962 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/10/2/142

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