Intraoperative Coronary Collateral Function in Patients With Coronary Occlusive Disease
Nitroglycerin Responsiveness and Angiographic Correlations

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SUMMARY
To elucidate the direct influence of nitroglycerin on coronary collateral function in patients and to clarify the relation between angiographic appearance and functional performance of coronary collaterals, we measured retrograde flow and peripheral coronary pressure (PCP) before and after nitroglycerin in patients undergoing saphenous vein bypass. Measurements were made via the distally (but not proximally) attached vein graft while the coronary artery receiving the graft was totally occluded proximal to the site of graft attachment. Nitroglycerin (100 to 150 mcg bolus and 100 mcg/min) was infused into the ascending aorta in 29 patients. Baseline measurements revealed: aortic pressure mean 79 mm Hg, PCP 30 mm Hg, retrograde flow 2.7 ml/min, and collateral resistance 28.5 mm Hg/ml/min. Following nitroglycerin, mean aortic pressure decreased 18% but retrograde flow was not consistently changed; thus collateral resistance fell significantly (average 28%, P < 0.05). Similarly, collateral resistance fell (mean 50%) in eight individuals in whom aortic pressure changes were attenuated by altering systemic flow. If calculated as a fraction of aortic pressure, PCP increased 9.9% (P < 0.02), a finding consistent with enhanced collateral flow. Our results suggest that nitroglycerin can diminish resistance to collateral flow despite severe multivessel involvement. Comparison of baseline data with preoperative angiography revealed a correlation between the size and extent of coronary collaterals and physiologic evidence of collateral function. Thus, angiographic appearance of coronary collaterals accurately predicts collateral function during bypass surgery.

Additional Indexing Words:
Myocardial ischemia Coronary arteriography Vasodilator Coronary bypass graft

The role of coronary collateral channels in the pathophysiology of coronary artery disease has been uncertain. This uncertainty is related, at least in part, to the lack of a direct assessment of coronary collateral function in humans. Radiosotope techniques have led to important advances in the evaluation of regional myocardial blood flow. However, changes in regional perfusion are not necessarily the result of alterations in coronary collateral function; many other factors are capable of influencing the distribution of myocardial blood flow. Angiographic and postmortem descriptions of coronary collateral anatomy frequently have been used to make inferences concerning the functional performance of coronary collateral channels. Yet these anatomic findings have not been previously correlated with physiologic function. In particular, angiographic assessment of coronary collaterals, an important part of the clinical evaluation of symptomatic coronary disease, has not been systematized by an objective, generally applicable grading system, nor have angiographic findings been compared with independently obtained estimates of coronary collateral function.

Uncertainty regarding the role of coronary collateral function contributes to uncertainty concerning the mechanisms responsible for the beneficial action of nitroglycerin (TNG) in patients with angina pectoris. A number of studies have sug-
suggested that TNG may augment blood flow to ischemic portions of the myocardium.\textsuperscript{14-17} Specifically, Fam and McGregor demonstrated that TNG was capable of reducing resistance to collateral blood flow in dogs with chronic coronary occlusions.\textsuperscript{14} Nevertheless, these animal data do not imply that TNG is equally capable of enhancing collateral blood flow in patients with multivessel coronary occlusive disease. On the contrary, several studies have emphasized TNG-induced changes in peripheral hemodynamics that tend to reduce myocardial oxygen requirements and have suggested that such an action comprises the major mechanism responsible for relief of ischemic pain.\textsuperscript{18-21} To help resolve these conflicting concepts and to further elucidate the action of TNG in patients, we sought direct measurement of the ability of TNG to influence physiological parameters of coronary collateral function in individuals with coronary disease. Aortocoronary bypass surgery has provided a unique opportunity to examine indices of coronary collateral function in humans with severe, symptomatic, multivessel coronary occlusive disease by permitting access to distal portions of the diseased coronary arterial tree.

In the following studies, we have utilized this opportunity to obtain information pertaining to two problems mentioned above: 1) Is nitroglycerin capable of exerting a direct effect on coronary collateral function in patients with multivessel coronary disease? and 2) How does angiographic evidence of the adequacy of coronary collaterals relate to a more quantitative assessment of collateral function?

Methods

Intraoperative studies were performed on 30 men and four women, aged 40 to 72 years (median 54), receiving saphenous vein bypass grafts because of angina pectoris that did not respond satisfactorily to medical management. These individuals represent a consecutive series of patients referred for surgical treatment; no attempt was made to select patients for study on the basis of preoperative clinical data. One patient had received an internal mammary artery implant two years previously, and another patient had removal of a ventricular aneurysm just prior to saphenous vein bypass grafting. No additional cardiac surgical procedures were performed in the other 32 individuals.

Of the 34 patients 23 (68%) had critical obstruction (>70% reduction in luminal diameter) present in all three major coronary arteries, nine (26%) had two-vessel disease, and two (6%) had single vessel disease. Eighteen (53%) had previously experienced one or more myocardial infarctions and 27 (80%) had an abnormal electrocardiogram prior to operation. Of the 28 with satisfactory left ventricular cineangiograms, 22 (79%) had regional or generalized abnormalities of contractile function. Typical angina pectoris had been present in all patients for one month to 25 years (median 10 months).

Nitrates and propranolol were discontinued in all patients at least 48 hours prior to operation. Anesthesia was induced with varying combinations of nitrous oxide, halothane, thiopental, and morphine sulphate. In addition, most patients also received curare and atropine sulphate. Median sternotomy was performed and cardiopulmonary bypass was instituted in a standard manner. The left ventricle was vented and mild systemic hypothermia induced (range 33.0-36.7°C, median 35.0°C). Ventricular fibrillation was produced by transient AC stimulation, and was sustained until defibrillation near the end of cardiopulmonary bypass. Studies were performed after the saphenous vein graft was anastomosed distally to the diseased coronary artery but before the graft was connected to the aorta. When incomplete proximal obstruction was present in the coronary artery receiving the graft, antegrade coronary flow (routinely arrested by a keeper to permit construction of the distal anastomosis) was restored for at least five minutes after graft attachment and prior to study.

Of the 34 grafts studied 18 (53%) were attached to the right coronary artery (RCA) or its posterior descending branch, 15 (44%) to the left anterior descending artery (LAD) and one (3%) to an obtuse marginal (OM) branch of the left circumflex artery. In the 28 patients receiving multiple bypass grafts, studies were performed utilizing the last graft to be placed in order to maximize the opportunity for collateral perfusion of potentially ischemic regions. Twenty-four patients had one additional graft (15 to the LAD, seven to the RCA and two to OM branches) and four had two additional grafts.

To obviate the influence of venous valves within the graft segment, pressure and flow data were obtained via a snugly fitting 3 mm inner diameter polyethylene catheter inserted into the saphenous vein graft (fig. 1). Care was taken to avoid distortion of the vein graft-coronary artery junction. The same atraumatic keeper (silastic tubing) used previously in the construction of the distal anastomosis was again secured proximally about the coronary artery to prevent antegrade flow. Measurement was then made of back pressure within the distal coronary artery (a quantity subsequently termed peripheral coronary pressure or PCP). Stable values were attained consistently within 15 seconds.

The accuracy of the aneroid manometers used to obtain simultaneous measurement of mean PCP and aortic pressure was ±2 mm Hg. The catheter within the vein graft was then vented to atmospheric pressure at the level of the coronary sinus, and retrograde flow from the distal coronary artery was collected for a period of 30 seconds to two minutes. No attempt was made to compensate for resistance within the catheter. In vitro studies using blood at comparable temperatures, however, showed a linear relation between pressure gradient across the catheter, ΔP (mm Hg) and flow, F

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Diagram of techniques used during intraoperative studies. After the vein graft was attached to the coronary artery but prior to its attachment to the aorta, a snugly fitting polyethylene cannula was inserted to obtain retrograde pressure and flow measurements. The outer end of the cannula was kept at the level of the right atrium. At the time of measurement antegrade coronary flow was temporarily halted by an atraumatic keeper except where complete occlusion was present due to atherosclerosis. Flow rate of the nitroglycerin infusion was insufficient to influence the measurement of aortic pressure.

\[ \Delta P = 1.1 + 0.29 F \] (\( r = 0.99 \)). Thus, pressure gradients in excess of 4 mm Hg due to the resistance of the cannula would be anticipated only in those five instances in which retrograde flow was greater than 10 ml/min.

After baseline measurement of PCP and retrograde flow, nitroglycerin was introduced into the ascending aorta as a bolus of 100-150 mcg followed by an infusion of approximately 100 mcg/min. A sterile solution of 100 mcg/ml nitroglycerin in saline was prepared immediately before each study by dissolving two 0.4 mg sublingual tablets freshly removed from sealed plastic containers (Eli Lilly and Co.), and passing the resultant solution through a Swinex millipore filter (0.22 \( \mu \)m). After achieving a stable decrease in aortic pressure (approximately one minute after initiation of intraaortic nitroglycerin), PCP and retrograde flow determinations were repeated. In eight patients, additional measurements were made after aortic pressure was adjusted to near control levels by altering the rate of systemic perfusion. The entire sequence of measurements required approximately five minutes.

All statistical processing of retrograde flow and calculated collateral resistance (aortic pressure/retrograde flow) was performed using logarithmically transformed data. The resulting unbiased suppression of scatter permitted standard statistical treatment of data in which raw baseline values spanned two orders of magnitude.

In the 24 patients with technically adequate preoperative coronary cineangiograms, collateral vessels to the coronary artery receiving the bypass graft used for intraoperative study were classified according to the grading system of Scherer et al.21a A synopsis of this grading system is given in table 1. Grading was performed by investigators who lacked any information regarding the patient's clinical status or intraoperative findings.

### Results

**Control Measurements**

Replicate determinations of PCP and retrograde flow showed close agreement in the absence of aortic pressure change. In nine replicate retrograde flow determinations mean difference between first and second values was 0.8% ± 9.7% (standard deviation). Infusions of the vehicle for TNG (lactose tablets in saline) were without effect on any of the parameters measured.

To evaluate the influence of aortic pressure change independent of any associated drug effect, pressure in the aorta was altered by changing the rate of systemic blood flow prior to administration of TNG. As shown in figure 2, calculated coronary collateral resistance fell as aortic pressure was raised, and conversely, a reduction in aortic pressure was associated with a consistent rise in collateral resistance. Measurements after return to baseline pressure in three patients indicated that these collateral resistance changes were largely reversible.

**Response to TNG**

When the rate of systemic perfusion was held constant, intraaortic administration of TNG was associated with a fall in aortic pressure in 27 of the 29 patients who were given TNG, the average change being a reduction of 15 mm Hg from a mean of 79 mm Hg (fig. 3, left). Retrograde flow, however, did not change consistently after TNG.

### Table 1

**Angiographic Grading of Collateral Vessels**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Opacification of the distal segment</th>
<th>Collaterals visualized</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>Faint</td>
<td>Few, small</td>
</tr>
<tr>
<td>2</td>
<td>Dense</td>
<td>many, small</td>
</tr>
<tr>
<td>3</td>
<td>Dense</td>
<td>one large (± many small)</td>
</tr>
<tr>
<td>4</td>
<td>Dense</td>
<td>two or more large (± many small)</td>
</tr>
</tbody>
</table>
TNG AND CORONARY COLLATERAL FUNCTION

Table 2

<table>
<thead>
<tr>
<th>Patient</th>
<th>Retrograde flow (ml/min)</th>
<th>Calculated collateral resistance mm Hg/ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>E.D.</td>
<td>9.0</td>
<td>10</td>
</tr>
<tr>
<td>G.G.</td>
<td>26.4</td>
<td>2.0</td>
</tr>
<tr>
<td>C.O.</td>
<td>0.2</td>
<td>460</td>
</tr>
<tr>
<td>J.S.</td>
<td>25.8</td>
<td>2.9</td>
</tr>
<tr>
<td>D.S.</td>
<td>4.8</td>
<td>15</td>
</tr>
<tr>
<td>H.B.</td>
<td>14.0</td>
<td>3.8</td>
</tr>
<tr>
<td>J.L.</td>
<td>7.2</td>
<td>8.3</td>
</tr>
<tr>
<td>W.H.</td>
<td>4.0</td>
<td>10.5</td>
</tr>
<tr>
<td>TNG</td>
<td>12.0</td>
<td>7.8</td>
</tr>
<tr>
<td>TNG</td>
<td>35.2</td>
<td>1.4</td>
</tr>
<tr>
<td>TNG</td>
<td>1.7</td>
<td>49</td>
</tr>
<tr>
<td>TNG</td>
<td>31.5</td>
<td>1.8</td>
</tr>
<tr>
<td>TNG</td>
<td>24.0</td>
<td>3.0</td>
</tr>
<tr>
<td>TNG</td>
<td>19.8</td>
<td>2.6</td>
</tr>
<tr>
<td>TNG</td>
<td>8.4</td>
<td>6.2</td>
</tr>
<tr>
<td>TNG</td>
<td>6.8</td>
<td>8.4</td>
</tr>
</tbody>
</table>

(fig. 3, right). Although measurements revealed a large range of baseline values for retrograde flow, there was no tendency for patients with particularly high or particularly low baseline values to respond to TNG in a distinctive manner.

Thus, retrograde flow was generally maintained despite a TNG-induced decline in aortic pressure, indicating an associated reduction in coronary collateral resistance. Calculation of collateral resistance showed that TNG administration was associated with a decrease in 23 of 29 patients; geometric averaging of resistances revealed a statistically significant \( P < 0.02 \) mean decrease of 28% (fig. 4, right). Although a broad range of baseline resistance was observed, the magnitude of the decrease in collateral resistance following TNG administration was essentially independent of baseline resistance (fig. 4, left).

As shown in figure 5, left, PCP exhibited a small but statistically significant \( P < 0.005 \) fall after TNG from an average baseline of 30 mm Hg to an average of 26 mm Hg. It is evident that PCP is heavily influenced by declining coronary perfusion pressure after TNG. This influence was attenuated by dividing absolute values of PCP by the simultaneously observed value of aortic pressure. These calculations revealed that TNG administration was associated with a modest but significant rise (averaging 9.9%, \( P < 0.02 \)) in PCP relative to aortic pressure (fig. 5, right). Like the fall in calculated collateral resistance, this rise in PCP relative to aortic pressure is consistent with a TNG-induced increase in the ability of collateral channels to deliver blood flow to potentially ischemic regions.

Ideally, assessment of the influence of TNG on coronary collateral function should be made in the absence of associated change in aortic pressure. Preliminary results indicated that TNG, when administered at rates insufficient to lower aortic pressure, also failed to alter coronary collateral resistance. Therefore, in eight patients TNG-induced reduction in aortic pressure was attenuated by adjustment of the rate of systemic blood flow (fig. 6, left). In contrast to results found when aortic pressure was permitted to fall, measurements after TNG with aortic pressure held constant revealed a consistent and sometimes dramatic rise in retrograde flow (fig. 6, middle, and table 2); and
Aortic Pressure

Figure 3

Comparison of aortic pressure (left panel) and retrograde flow before (BASE) and after TNG. Because of the great spread in baseline values, a logarithmic scale is used for retrograde flow. TNG produced a fall in aortic pressure in 27/29 studied, mean decrease being 15 mm Hg (P < 0.001). Mean values for aortic pressure are denoted by symbols on either side of the left panel. In contrast to aortic pressure, retrograde flow showed no net change, although large increases and decreases were found in individual cases. Geometric means, for retrograde flow, shown on either side of the right panel, were 2.7 ml/min baseline and 2.9 ml/min after TNG.

Angiographic and Clinical Correlations

Of the 24 patients with adequate preoperative coronary cineangiograms, seven were found to have no visible collaterals (Grade 0), 12 had two or more large collaterals (Grade 4) and the remaining five were divided among three intermediate categories. Patients with no visible collaterals on the angiogram had the least evidence of coronary collateral function, as assessed by baseline intraoperative measurements (fig. 7): mean PCP/aortic pressure was 0.24; mean retrograde flow was 0.83 ml/min; and mean calculated collateral resistance was 94 mm Hg/ml/min. In contrast, patients with maximal coronary collaterals (Grade 4) had significantly (P < 0.05) greater mean values for PCP/aortic pressure (0.50) and retrograde flow (15.7 ml/min) and significantly smaller mean collateral resistance 5.1 mm Hg/ml/min). Intermediate angiographic grades generally tended to have intermediate values for retrograde flow and collateral resistance. Thus, increasing coronary collaterals, as revealed by the angiogram, were associated with better coronary collateral function, as assessed by intraoperative pressure and flow measurements. Responsiveness to TNG, as evaluated by percent reduction in coronary collateral resistance, was not correlated with angiographic appearance of collaterals. Hence, large coronary collaterals did not appear more capable of facilitating coronary flow after TNG (at
least in terms of percent change) than smaller collaterals.

There was, in general, no correlation either of TNG responsiveness or of baseline values with clinical status that explained the considerable spread of the data. The single exception to this statement was a relation between percent fall in collateral resistance after TNG and the duration of anginal symptoms prior to operation (fig. 8). None of the seven patients with angina for less than six months had TNG-induced decreases in collateral resistance in excess of 30%, yet declines of greater than 30% were seen in nine of 21 patients with angina for more than six months ($P < 0.05$).

Baseline measurements indicated significantly ($P < 0.05$) better baseline collateral function (higher PCP/aortic pressure and retrograde flow and lower collateral resistance) and a tendency toward greater responsiveness to TNG in the 12 patients with complete proximal atherosclerotic occlusion in the coronary artery receiving the bypass graft used for study. Six patients did not receive bypass grafts in addition to the graft used for study. The mean fall in collateral resistance after TNG in these patients (21%) was essentially the same as the mean for the entire group. Thus, there is no indication that the observed TNG effects required the presence of a functioning bypass graft to coronary vessels other than the one being studied. The one patient with an anterior internal mammary implant several years prior to bypass surgery had a 32% rise in resistance to collateral flow to the LAD following TNG. This atypical response may reflect altered properties of collaterals influenced by the internal mammary implant. There was no discernible difference between studies conducted with grafts to the LAD as compared to studies of grafts to the RCA.

**Discussion**

Measurements of PCP and retrograde flow have long been used to evaluate coronary collateral
Peripheral coronary pressure (PCP) is shown in mm Hg (left panel) and expressed as a fraction of simultaneous aortic pressure (right panel) before (BASE) and after TNG. Means are denoted by circled bars on either side of each panel. TNG administration was associated with a small but significant decline in PCP from a mean of 30 mm Hg to 26 mm Hg (P < 0.005). PCP/aortic pressure rose significantly, however, from a mean of 0.39 to 0.43, (an increase of 9.9%, P < 0.02). This finding is consistent with a TNG-induced decrease in resistance to collateral flow.

Recently, the validity of these techniques has been questioned because of apparent discrepancies with radioisotope washout data. Isotope washout studies are, themselves, not without theoretical and practical drawbacks. It should also be noted, however, that important conceptual differences distinguish retrograde flow techniques from isotope studies of myocardial perfusion. Measurements of retrograde flow and calculated collateral resistance reflect the ability of interarterial anastamotic channels to deliver blood flow to the distal portion of an occluded artery when this anastamotic system is maximally (and artificially) stressed by reducing pressure in the distal segment to atmospheric levels. Thus, unlike isotope washout, retrograde flow is not a direct measure of regional tissue perfusion. Rather, it evaluates a functional capacity which may be called upon, to a greater or lesser degree, during periods of ischemic insult. The responsiveness of this functional capacity to TNG and the relation of this functional capacity to its anatomic analog, the presence of collaterals on angiogram, are the subjects of the present investigation.

In our control studies a purely mechanical reduction in aortic pressure consistently resulted in a rise in calculated coronary collateral resistance. This may reflect either a direct effect of pressure reduction on small blood vessels or a reflexly-mediated response to systemic hypotension. In either case, if TNG were devoid of direct effects on the coronary circulation and (under the circumstances of study) only produced a fall in aortic blood pressure as a result of systemic vasodilation, one would anticipate a consistent rise in collateral resistance after patients received TNG. The fact that TNG administration was associated with a significant fall in collateral resistance implies that
TNG exerted a direct facilitating effect on channels conducting collateral flow. This concept is supported by the consistent and marked rise in retrograde flow and fall in collateral resistance after TNG when aortic pressure was mechanically maintained at control levels. It also is supported by the small but significant rise in the ratio of PCP/aortic pressure after TNG. The rise in PCP/aortic pressure following TNG may have been less marked than the changes in collateral resistance due to a TNG-induced increase in capillary runoff from the distal segment of the occluded artery.

Our findings are consistent with similar studies performed by Fam and McGregor in chronically ischemic dogs and also with the intraoperative studies of Horowitz and coworkers demonstrating increased rate of xenon washout from chronically ischemic portions of the human heart following TNG. Our results suggest that one possible explanation for this TNG-induced enhancement of xenon washout rate may be an augmentation of tissue perfusion due to a decline in resistance to collateral flow.

Although they are consistent with previously published reports, the results of this study must still be interpreted with considerable caution. Our observations were made in the mildly hypothermic, fibrillating, emptied hearts of anesthetized patients. These circumstances may be helpful in that they eliminate the mechanical effects of systole, permitting steady-state retrograde flow measurements and they also greatly reduce the possibility of peripherally mediated action of TNG. Nevertheless, collateral channels may be subjected to a number of metabolic, mechanical, and pharmacologic influences not present under the ordinary circumstances of TNG use. Furthermore, the concentration of TNG achieved in the coronary arteries (although a minimum effective dose in this study) may be considerably in excess of that reached with conventional modes of TNG therapy. Finally, it should be noted that our studies do not
Peripheral coronary pressure, expressed as a fraction of aortic pressure (left panel), retrograde flow (middle panel) and calculated coronary collateral resistance (right panel) are each related to the angiographic appearance of collaterals supplying the vessel under study. Grade 0 denotes no visible collaterals, Grade 4, two or more large collaterals, and Grades 1-3, intermediate collateralization, as defined in the text. Short horizontal lines denote mean values and brackets indicate standard error. Results of an analysis of variance are given at the top of each panel. In general, higher angiographic grades were associated with greater values for PCP/aortic pressure and retrograde flow and lower values for collateral resistance.

localize the site of TNG action: a reduction in resistance to blood flow may have occurred either within fine intercoronary anastomotic vessels or within the larger coronary arteries supplying these vessels (the possibility that the observed effects of TNG were mediated entirely by actions on the fresh grafts or their connections was eliminated).

Despite the limitations and uncertainties just outlined, our data indicate that TNG is capable of expediting blood flow to potentially ischemic regions via collateral channels in humans with severely symptomatic, multivessel coronary occlusive disease. These findings emphasize the possibility that this salutary effect on channels conducting coronary collateral flow may play a significant role in the ordinary therapeutic actions of TNG.

Comparison of preoperative angiograms and intraoperative data indicate that the radiographic appearance of coronary collaterals bears a close and consistent relationship to the functional capacity of these collaterals. This finding implies that angiography is useful not only in documenting the extent and location of coronary occlusive disease but may also be useful in assessing the relative degree of collateral function available to potentially ischemic regions. These results substantiate similar preliminary findings of Gensini et al.27 The correlation of baseline physiologic measurements and angiographic findings also suggests that at least part of the variability encountered in baseline physiologic measurements is explained by large differences in extent and size of collateral vessels. In a preliminary communication Williams et al. reported that in patients receiving bypass grafts a direct relation existed between intraoperative retrograde flow and PCF and the severity of proximal stenosis, as assessed by gradient measurement and preoperative angiogram.28 These findings, confirmed by our own results, emphasize the importance of severity of proximal coronary obstruction in the genesis of collateral channels.

Our data indicate that greatest degrees of TNG responsiveness were encountered exclusively in individuals with angina pectoris for at least six months. Duration of anginal symptoms seemed to be more important than angiographic appearance of collaterals in determining the percent fall in coronary collateral resistance after TNG. Although the correlation of TNG responsiveness with duration of angina may reflect subtle factors in patient
Comparison of percent change in calculated coronary collateral resistance after TNG in those seven patients with typical angina pectoris for less than six months and in those 21 patients with angina for more than six months. Means are denoted by horizontal bars. None of the patients with angina for less than six months had a decrease in excess of 30%, but 8/21 of those with angina for more than six months had decreases greater than 30% (P < 0.05). Thus, the largest responses to TNG were seen only in patients with angina for more than six months.

selection, it is also possible that maximal TNG responsiveness is achieved only after suitable structural development or biochemical evolution of coronary collateral channels in response to ischemic stress.

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