Determinants of Collateral Filling Observed During Sudden Controlled Coronary Artery Occlusion in Human Subjects

MARC COHEN, MD, FACC, WARREN SHERMAN, MD, FACC, K. PETER RENTROP, MD, FACC,* RICHARD GORLIN, MD, FACC

New York, New York

Higher grades of collateral circulation limit the extent of myocardial ischemia observed during balloon inflation in patients with single vessel coronary disease undergoing coronary angioplasty. However, the grade of collateral filling during sudden coronary occlusion varies from patient to patient. To assess which characteristics may predict a high grade of collateral filling, baseline clinical and angiographic variables were correlated with the grade of filling during coronary occlusion in 67 patients (whose angina ranged from 1 week to 36 months in duration) undergoing left anterior descending or right coronary artery angioplasty. A second contralateral arterial catheter was used to assess the collateral filling that reached the vessel dilated before and during transient total occlusion by the angioplasty balloon.

Thirty-six patients had a proximal stenotic lesion ranging in severity from 65 to 99%. On a 0 to 3 scale, mean collateral filling grade before inflation was 0.4 versus 1.8 during inflation (p = 0.001). All 19 patients with 95 to 99% stenosis had at least grade 2 collateral filling during inflation. In contrast, 18 of 21 patients with ≤80% stenosis had only grade 0 or 1 collateral filling during inflation. There were significant positive correlations between collateral grade during inflation and 1) baseline lesion severity (r = 0.76), 2) baseline collateral filling grade (r = 0.50), and 3) vessel dilated. There was no relation between collateral filling during inflation and age, gender, risk factors, duration of angina or proximal versus distal location of the lesion. Lesion severity was the only independent variable associated with collateral filling grade.

Among the baseline variables available before angioplasty, lesion stenosis is the best predictor of collateral flow reserve. The percent stenosis present before myocardial infarction and the associated collateral reserve may explain some of the variability in infarct size observed after acute coronary artery thrombosis. (J Am Coll Cardiol 1989;13:297-303)
Methods

Study patients. The principles of patient selection, premedication, collateral visualization before, during and after angioplasty, as well as the grading of the degree of collateral filling, have been described in previous publications (1,5). In this study, patients were prospectively selected from 1,135 consecutive patients undergoing elective transluminal coronary angioplasty of the left anterior descending or right coronary artery. Inclusion criteria were 1) history of angina pectoris and no previous transmural myocardial infarction; 2) right dominant coronary circulation and single vessel coronary artery disease in either the left anterior descending or the right coronary artery; and 3) normal left ventricular function. Exclusion criteria were 1) moderate to severe hypertension (diastolic pressure >95 mm Hg), anemia, previous cardiac surgery, renal insufficiency or bleeding diathesis; 2) peripheral vascular disease limiting arterial access; and 3) electrocardiographic (ECG) evidence of left ventricular hypertrophy, left ventricular wall motion abnormalities involving >5% of the diastolic perimeter in the right anterior oblique view on baseline ventriculogram, and total occlusion of the angioplasty vessel. Sixty-seven patients met these criteria and gave informed consent for the additional catheters and contrast injections. This study was approved by institutional review board of the Mount Sinai Hospital.

The same observer (M.C.) obtained the medical history and performed the clinical examination at the time of admission of all patients. The following variables were recorded: age, gender, race, diabetes mellitus, cigarette smoking, mild hypertension, duration of symptoms of angina pectoris from first onset in life to the time of angioplasty, presentation as stable versus unstable angina and current medications. In addition, serum glucose and cholesterol, hematocrit and baseline ECG variables were noted. Summary statistics regarding the clinical and baseline angiographic characteristics of the 67 study patients are presented in Table 1. The first 23 patients were presented, in part, in a prior investigation (14).

Cardiac catheterization and angioplasty. All patients in this study received the following medications: diprydiamole (75 mg) and aspirin (325 mg) orally the night before the procedure and again the following morning before the procedure and oxazepam (? mg orally and 2 mg intramuscularly as premedication). During the catheterization, nifedipine (10 mg) sublingually followed by an intravenous infusion of nitroglycerin titrated to maintain the mean arterial pressure between 80 and 100 mm Hg.

Catheter systems and hemodynamics. Either a Stertzer brachial guiding catheter (USCI) or a femoral guiding catheter was used to guide the angioplasty balloon catheter. The balloon dilation catheters and guide wires were either manufactured by USCI or ACS. A 5F right or left Judkins coronary arteriography catheter (Cook) was advanced through a 5F sheath placed in the left femoral artery. Aortic and distal coronary artery pressure and heart rate were recorded on a Honeywell Electronics for Medicine recording console. In 45 patients in whom USCI balloons were used, the translesional gradient before dilation was measured.

Angiography and grading of collateral filling. The severity of coronary stenosis was evaluated by two readers measuring the percent reduction in luminal diameter from a magnified image of the cinearteriogram (15). Lesions more severe than 90%, in which the column of contrast medium was interrupted but there was complete and brisk filling of the distal vessel, were characterized as 95% stenoses; lesions in which the column of contrast medium was interrupted and distal filling was slow were characterized as 99% stenoses (15). Lesions in the right coronary artery before the acute marginal branch or of the left anterior descending artery before the first large septal perforator were considered proximal. The grading scale used to quantify the extent of collateral channel filling has been previously described (1); grade 0 = no visible filling of any collateral channels; grade 1 = filling by collateral channels of branches of the vessel dilated, without any contrast medium reaching the epicardial segment of that vessel; grade 2 = partial filling through collateral channels of the epicardial segment of the vessel dilated; and grade 3 = complete filling of the vessel dilated by collateral channels. Cine films were analyzed in a random sequence by two angiographers who were not involved with the angioplasty.

Study protocol. Cycle 0, baseline. With the use of a 5F coronary catheter, arteriograms of the contralateral artery were performed. In orthogonal views, allowing assessment of the degree of collateral filling immediately before angioplasty. Thereafter, multiple views of the stenosed vessel to be dilated were obtained through the guiding catheter; the deflated angioplasty balloon was guided across the lesion.
and a gradient obtained. Routine angioplasty proceeded with two inflations. Just before the balloon was deflated during the second inflation, contrast medium was injected through the guiding catheter to document the absence of flow around the inflated balloon and the absence of intracoronary collateral filling. Several minutes after recovery from these initial inflations additional inflations were performed during which the "study" variables were measured.

Cycle 1. Immediately before and throughout balloon inflation simultaneous aortic and distal coronary artery pressure and heart rate were recorded. At 40 s into balloon inflation, an arteriogram of the contralateral artery was obtained.

Cycle 2. Before removal of the balloon catheter, simultaneous aortic and distal coronary artery pressures were recorded. After removal of the catheter, arteriography of the contralateral artery was repeated.

Statistics. All continuous variables are presented as the mean values ± SD. The examination of differences between continuous variables in the study cycle and the control cycle (cycle 0) involved the Student's paired t test. The nonparametric statistic, the Spearman rank correlation coefficient, was used to test the relation between collateral filling grade (measured on a nominal scale from 0 to 3), and continuous baseline variables (age, duration of angina, lesion percent stenosis). The chi-square statistic and the Fisher exact test were used to test the association between dichotomous variables (gender, race, smoking, diabetes, hypertension, unstable angina, vessel dilated, lesion location) and the collateral grade during inflation. For this analysis, patients with collateral filling grade 0 or 1 were combined and compared with patients with grade 2 or 3 filling. Logistic regression analysis was used to identify variables independently correlating with collateral grade during balloon inflation.

Results

In all 67 patients angioplasty produced a reduction in the severity of stenosis to <30% narrowing in luminal diameter. In addition, the mean translesional gradient was reduced to ≤15 mm Hg in all 45 patients in which it was measured. During balloon occlusion, heart rate increased from 67 ± 6 to 75 ± 13 beats/min, and mean aortic pressure decreased slightly from 87 ± 8 to 84 ± 4 mm Hg.

Changes in collateral filling during coronary occlusion (Fig. 1). Baseline arteriography of the contralateral vessel revealed a mean collateral filling grade of 0.4 ± 0.7. Forty eight patients had a collateral filling grade of 0, 11 had grade 1 and 8 had grade 2 filling. During balloon inflation, there was a significant increase in the mean grade of collateral filling to 1.8 ± 1.0 (p < 0.01); the mean change was 1.4 ± 0.9. Eleven patients had no change in grade; 9 of these 11 had collateral filling grade 0 before angioplasty. Collateral filling improved by at least one grade in 56 (84%) of the 67 patients and by at least two grades in 28 patients (42%). In 25 patients who originally had no visible collateral channels, collateral filling increased to grade 2 or 3. Arteriography after the stenosis was dilated and the balloon catheter removed revealed no collateral filling to the dilated vessel in any patient.

Correlates of collateral grade during occlusion (Table 2). Clinical variables. No clinical variables (gender, race, smoking, diabetes, hypertension or unstable angina) correlated with the grade of collateral filling observed during occlusion. In addition, neither of the two clinical variables often associated with increased collateral circulation (age and duration of angina symptoms) correlated with collateral grade. Figure 2 shows the broad range of symptom duration before angioplasty observed with each collateral grade. Even in the 38 patients with a ≥90% stenosis, there was no correlation between collateral grade and duration of angina symptoms.

Angiographic variables. No significant association was observed between the baseline translesional gradient and the proximal versus distal location of the stenosis. In contrast, there was a weakly positive correlation between collateral filling grade before angioplasty and the grade during occlusion (Spearman r = 0.50, p < 0.01). Furthermore, a right coronary lesion (as opposed to a lesion in the left anterior descending artery) and a lesion severity ≥90% were significantly associated with a higher collateral grade during occlusion (p = 0.01 and p = 0.001, respectively). Logistic regression analysis, however, revealed that lesion severity before angioplasty was the only independent variable significantly correlated with collateral grade.

In fact, the distribution of percent stenosis versus collateral filling grade (Fig. 3), suggests a significant stepwise correlation (Spearman r = 0.76, p = 0.002), in which the collateral grade increases as the percent stenosis before angioplasty increases. Eighteen of the 21 patients with ≥80%
Table 2. Clinical and Angiographic Characteristics of 67 Patients in Relation to Collateral Filling Grade During Occlusion (dichotomous variables)

<table>
<thead>
<tr>
<th>Clinical variables</th>
<th>Collateral Grade During Inflation</th>
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<tbody>
<tr>
<td>Gender</td>
<td>0 or 1</td>
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<tr>
<td>Male</td>
<td>19</td>
</tr>
<tr>
<td>Female</td>
<td>5</td>
</tr>
<tr>
<td>Race</td>
<td></td>
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<tr>
<td>White</td>
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</tr>
<tr>
<td>Black</td>
<td>4</td>
</tr>
<tr>
<td>Smoker</td>
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</tr>
<tr>
<td>No</td>
<td>10</td>
</tr>
<tr>
<td>Yes</td>
<td>14</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>21</td>
</tr>
<tr>
<td>Yes</td>
<td>3</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>17</td>
</tr>
<tr>
<td>Yes</td>
<td>7</td>
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<tr>
<td>Unstable angina</td>
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</tr>
<tr>
<td>No</td>
<td>11</td>
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<tr>
<td>Yes</td>
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<table>
<thead>
<tr>
<th>Angiographic variables</th>
<th>Collateral Grade Before Angioplasty</th>
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</thead>
<tbody>
<tr>
<td>Vessel dilated</td>
<td>0 or 1</td>
</tr>
<tr>
<td>LAD</td>
<td>21</td>
</tr>
<tr>
<td>RCA</td>
<td>3</td>
</tr>
<tr>
<td>Lesion location</td>
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<tr>
<td>Proximal</td>
<td>13</td>
</tr>
<tr>
<td>Distal</td>
<td>11</td>
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<tr>
<td>Lesion severity &lt;90%</td>
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<tr>
<td>≥90%</td>
<td>4</td>
</tr>
<tr>
<td>Collateral grade before angioplasty</td>
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<tr>
<td>0 or 1</td>
<td>24</td>
</tr>
<tr>
<td>2 or 3</td>
<td>0</td>
</tr>
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</table>

*Significant difference by univariate analysis; *remains significant in the stepwise regression analysis. Abbreviations as in Table 1.

Discussion

Factors stimulating collateral development. Animal studies. In 1936, Wiggers (16) postulated that "the slow establishment of differential pressure gradients during development of partial or complete occlusion of a main branch may distend normally useless vessels [small collaterals] ... to a degree that they soon become pervious to blood." Eckstein (17) observed that "the extent of collateral blood flow was proportional to the degree of constriction," but suggested that "a pressure differential and decreased coronary flow are both necessary for collateral growth." More definitive experiments by Khouri et al. (18) and Elliot et al. (19) indicated that an arterial constriction resulting in a pressure gradient between the two distal coronary beds was essential for collateral growth. The constriction that causes the small pressure gradient is enough to decrease reactive hyperemia but is not severe enough to reduce resting inflow.

In contrast, more recent experimental work has suggested that factors other than a fixed resting pressure gradient may also contribute to collateral flow development.

Figure 2. Relation between the duration of anginal symptoms and the collateral filling grade during occlusion in 67 patients.

Figure 3. Relation between the percent luminal stenosis before angioplasty (stenosis pre) and the collateral grade during occlusion in 67 patients.
Yamamoto et al. (20) observed that repeated, brief coronary occlusion was an adequate stimulus for collateral growth in a dog model. Furthermore, the experiments of Schwarz et al. (21) suggested that genetic differences among individual dogs were a major determinant of the response of native small congenital anastomoses to the well-established stimulus of a constrictor causing a pressure gradient.

**Human Studies on Factors Stimulating Collateral Development**

Autopsy studies have established the presence of small (50 to 250 μm) intercoronary anastomoses in practically all normal human hearts (22–24). Several factors, such as coronary occlusion, anemia or hypoxia, have been identified that stimulate the growth of these small channels into larger ones (>500 μm) capable of protecting ischemic myocardium.

**Role of coronary stenosis or occlusion or both.** Studies by Schwartz et al. (10) and Nitzberg et al. (11) document the serial growth in collateral channels induced by sudden total coronary occlusion. Immediately after occlusion, only 5 to 10% of patients have large collateral channels. Within 2 to 3 weeks, augmentation occurs resulting in large collateral vessels in >50% of patients. In patients with coronary spasm, recurrent episodes of transient severe narrowing or even total occlusion of a coronary artery has also been associated with good collateral growth (25,26). These findings suggest that a major role for a pressure differential as a stimulus for collateral growth in human subjects is in accord with the experimental observations described. Although it is clear that total occlusion is an effective stimulus for collateral channel growth, the data correlating different grades of coronary stenosis (<100%) with the augmentation in collateral flow are less clear. Gensini and da Costa (27) observed angiographic evidence of collateral filling (>100 to 200 μm channels) only in patients with a >90% stenosis. In addition, a few case reports (28,29) have shown that patients with a subtotal stenotic lesion may demonstrate good collateral filling immediately after the lesion progresses to total occlusion. A recent report by Rentrop et al. (14) suggests that patients with >70% stenosis are likely to have some collateral flow after sudden coronary occlusion.

**Present study.** This study describes the first large scale (67 patients) prospective analysis associating severe coronary stenosis with good collateral circulation immediately after sudden total occlusion in patients with coronary artery disease. In the absence of severe stenosis (>80%), only three patients had significant collateral filling. In contrast, all patients with a ≥95% stenosis had well developed collateral filling. The difference in the threshold value for collateral development with regard to lesion severity between our study and the prior study of Rentrop et al. (14) could be related to variability in techniques of assessing stenosis severity. Our study also found no correlation between the duration of symptoms and the grade of collateral filling. Several patients with sudden onset of symptoms had extensive collateral circulation whereas others with several months of angina pectoris but a less than critical stenosis had minimal collateral filling. This is in distinct contrast to the observations made by Fulton (30) that suggest a strong relation between time and size of collateral channels. In keeping with the prior observations of Ilcic et al. (31), we also did not observe any correlation between coronary risk factors and collateral filling.

Our findings of good collateral filling in patients with short duration of symptoms but with a severe coronary lesion raises the possibility of genetic predisposition, as do other reports documenting large intercoronary channels in the absence of occlusive coronary disease (32–34). In addition, our study excluded patients with severe but less than totally occlusive coronary disease who had sustained myocardial infarction. There is a subset of patients with critical coronary stenosis who, during angioplasty balloon occlusion, experienced severe angina and ECG evidence of ischemia, suggesting that the presence of severe stenosis did not trigger prior collateral growth. These latter observations prompt the consideration of factors other than coronary stenosis alone as stimuli for collateral growth in human subjects. Combining our own observations with the findings of prior investigators, we submit the following hypotheses regarding collateral development in human subjects.

**Mechanisms of collateral channel development.** All human beings have substantial interarterial coronary anastomoses in utero. In the majority of the neonates, these large channels involute after birth (35,36). Sudden coronary occlusion, in the absence of any preexisting stimuli for collateral growth, will therefore result in substantial myocardial damage. However, the sudden decrease in distal coronary pressure, compared with that in neighboring vessels, resulting from total occlusion will, over the span of 2 weeks, stimulate collateral growth. Apart from the severe pressure gradient induced by sudden total occlusion, the pressure gradient at rest induced by a 90 to 99% stenosis also appears to be adequate to stimulate collateral growth. In contrast to dogs, in which a small pressure gradient is sufficient to stimulate collateral channels, the gradient in humans has to be severe enough to correlate with a reduction in inflow at rest to trigger collateral growth.

In a small minority of patients the involution of collateral channels may be incomplete. In this subset of patients, sudden plaque rupture resulting in severe luminal stenosis within a short span of time immediately opens present but underutilized collateral channels. This subset would, for example, include our patients with good collateral filling but a very short duration of symptoms.

**Clinical implications.** Adults experiencing a large myocardial infarction probably have sustained sudden total occlusion at the site of what was previously only a moderately...
severe (<80%) stenosis. Patients with a severe preexisting coronary stenosis (>90%) of some duration (12.37–39) are better prepared to handle sudden progression to total occlusion and present with good collateral scores and a small infarct size or non-Q wave infarction.

Limitations of study. Patients received the vasodilators nitroglycerin and nifedipine before assessment of collateral channels. However, aortic pressure did not significantly change between the different study cycles and, in keeping with recent reported observations (3,40), it is unlikely that these vasodilators had a significant effect on our observations. In addition, we did not evaluate absolute flow through the collateral channels. In lieu of flow measurement, we applied a grading scale for collateral filling that was developed and validated (1) and correlates well with left ventricular function after sudden coronary occlusion (5).

Conclusions. In a high percentage of patients with coronary artery disease collateral filling is augmented during sudden coronary occlusion, thereby demonstrating collateral flow reserve. Among the baseline variables available before angioplasty, lesion stenosis is the best predictor of collateral reserve. The percent stenosis before myocardial infarction and the associated collateral reserve may explain some of the variability in infarct size observed after acute coronary artery thrombosis.

We gratefully acknowledge Valentin Fuster, MD, Chief of the Division of Cardiology, for support and suggestions, and John Ambrose, MD for assistance with several of the study patients.

References


