Limitation of myocardial ischemia by collateral circulation during sudden controlled coronary artery occlusion in human subjects: a prospective study

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ABSTRACT We have shown improvement in collateral filling immediately after sudden controlled coronary occlusion in human subjects undergoing elective coronary angioplasty. It has been suggested but not proved that collateral circulation can limit myocardial ischemia. We prospectively studied 23 patients with isolated left anterior descending (n = 14) or right coronary (n = 9) disease and normal left ventriculograms during elective coronary angioplasty. A second arterial catheter was used for injection of the contralateral artery to assess collateral filling before balloon placement and during coronary occlusion by balloon inflation. Left ventriculography was performed during another inflation. Grading of collateral filling was as follows: 0 = none, 1 = filling of side branches only, 2 = partial filling of the epicardial segment, 3 = complete filling of the epicardial segment. Indexes of myocardial ischemia included percent of the left ventricular perimeter showing new hypocontractility and the sum of ST segment elevation measured on a simultaneous 12-lead electrocardiogram recorded during each inflation. Collateral filling during balloon occlusion and indexes of ischemia were assessed at 30 to 40 sec into inflation. Aortie pressure and heart rate did not correlate with the percent hypocontractile perimeter nor the sum of ST segment elevation. There was a significant correlation between the grade of collateral filling during inflation and both percent hypocontractile perimeter (r = −.85) and the sum of ST segment elevation (r = −.87). Anginal pain occurred in all patients with grade 0 or 1 collateral filling but in only 36% of patients with grade 2 or 3 collaterals. In conclusion, collateral circulation limits myocardial ischemia as assessed by the extent of new ventricular asynergy and electrocardiographic changes during coronary occlusion in patients.


THE ABILITY of collateral circulation to limit myocardial ischemia and prevent infarction has been a matter of considerable debate. Initially, pathologic evaluation of postmortem hearts of patients with chronic ischemic heart disease suggested that a significant number of patients had sustained total coronary occlusion without ischemic injury presumably because of collateral flow to the jeopardized zone.1-3 With the advent of selective coronary arteriography, many investigations used angiographic techniques to elucidate the functional significance of collateral circulation in vivo in patients with chronic ischemic heart disease.1-9 These studies, however, left the matter unresolved.

More recently, the impact of collateral circulation during the acute phase of myocardial infarction has been assessed.10-12 Several of these studies suggested that the presence of collaterals in the early hours of acute infarction was associated with relatively smaller infarcts. However, these studies were limited by the fact that the patients presented several hours after total occlusion of the infarct-related artery, very little information was available regarding the clinical and coronary arteriographic characteristics of the patients before infarction, and additional therapeutic interventions were often employed that may have also limited infarct size.

Patients with coronary artery disease undergoing elective percutaneous transluminal coronary angioplasty (PTCA) provide a model for prospective evaluation of the functional significance of collateral circulation in the setting of sudden coronary artery occlusion. By means of a second arterial catheter for contrast injections of the contralateral coronary artery during...
balloon occlusion, we have previously shown that in a high percentage of patients with severe coronary stenosis, collateral channel filling improves within 60 to 90 sec after balloon occlusion. In the present study, we used a second arterial catheter for contrast injection of the contralateral coronary artery during one balloon inflation and left ventriculography during another inflation. In this fashion, we prospectively studied 23 patients to assess the degree of collateral circulation to the dilated artery and to correlate this with the degree of ventricular dysfunction observed during sudden coronary occlusion.

Methods

Patients. The principles of patient selection, premedications, collateral visualization before, during, and after PTCA, and the grading of the degree of collateral filling have been described in previous publications. In the present study, patients were prospectively selected from 142 consecutive patients undergoing elective PTCA. All patients had (1) single-ventricle coronary disease of either the left anterior descending or a dominant right coronary artery and (2) normal global and segmental left ventricular function. Patients with the following characteristics were excluded: (1) history of hypertension (diastolic pressure above 90 mm Hg), additional noncoronary cardiac disease, chronic obstructive lung disease, anemia, bleeding diathesis, or baseline ST segment elevation or depression of greater than 1 mm or (2) peripheral vascular disease compromising arterial access, or renal insufficiency. Twenty-four patients met the above criteria and gave informed consent to receive the additional catheters and contrast injections. This study was approved by the Mount Sinai Hospital institutional review board. One patient was excluded from the analysis because a large diagonal branch originating before a mid left anterior descending artery stenosis was completely obstructed during balloon inflation. The baseline clinical and angiographic characteristics of the remaining 23 patients are described in Table 1.

Cardiac catheterization and angioplasty protocol

Medications. Dipyridamole (75 mg orally) was given the night before the procedure. Dipyridamole (75 mg), aspirin (325 mg), and oxazepam (Lorazepam, 2 mg orally and 2 mg im) were given as premedication. Immediately before insertion of the catheters, nifedipine (10 mg sublingually) was given, followed by a continuous intravenous infusion of nitroglycerin titrated to maintain the mean arterial pressure between 80 and 100 mm Hg.

Catheter systems. A Stertzter balloon angioplasty guiding catheter (USCI) was advanced via the right brachial artery. Balloon dilatation catheters and guidewires (USCI) of variable sizes were used as clinically indicated. A No. 5F right or left Judkins coronary arteriography catheter (Cook) and a No. 5F pigtail catheter (Cook) were sequentially advanced through a No. 5F sheath placed in the left or right femoral artery. The Judkins coronary catheters were used to inject the contralateral artery (the right if the lesion was in the left anterior descending artery, or the left if the lesion was in the right coronary artery). The No. 5F pigtail catheter was used for left ventriculography.

Hemodynamics and electrocardiography. Simultaneous aortic pressure, peripheral coronary artery pressure, and left ventricular pressure were measured with fluid-filling tubing and Statham P231D pressure transducers. Heart rate was calculated from a Honeywell Electronics for Medicine recording console. Standard 12-lead electrocardiograms were recorded at 25 mm/sec paper speed with a Hewlett Packard 4700A Pagewriter.

which acquires all 12 leads within 10 sec. ST segment elevation above baseline (as defined by the preceding PR segment) was measured to the closest 0.5 mm 0.02 sec after the J point. ST segment depression was measured to the closest 0.5 mm 0.08 sec after the J point. The sum of ST segment elevation occurring during balloon occlusion of the coronary artery was calculated from the 12-lead electrocardiogram by summing the ST segment elevation in each of the 12 leads.

Angiography and grading of collaterals. The severity of coronary stenosis was evaluated by measuring the percent reduction in lumen diameter from a magnified image of the cineangiogram. Lesions of 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. Each of the 23 patients had three contrast injections of the contralateral artery (before intervention, during inflation, and after intervention). Evaluation of the grade of collateral filling observed during each of the 69 injections was made by a panel of two angiographers, who saw the injections in a random order and without knowledge of which patient was being presented. Briefly, grade 0 = no visible filling of any collateral channels (figure 1), grade 1 = filling by means of collateral channels of side branches of the vessel being dilated but without any dye reaching the epicardial segment of that vessel, grade 2 = partial filling via collateral channels of the epicardial segment of the vessel being dilated, and grade 3 = complete filling of the vessel being dilated (figure 2). The reproducibility of this grading system has been validated in our prior publication.

The Diasonics/Fischer digital subtraction imaging system was used for creation and analysis of the left ventricular images obtained in the right anterior oblique view by injection of 40 ml of Renografin 38% contrast directly into the left ventricle. Left ventricular ejection fraction was calculated by the area length method of Dodge et al. The extent of segmental wall motion abnormalities was quantified by the radial axis model of Ingels et al. In this model, radii are spaced 5 degrees apart around the centroid and radial shortening less than 2 SD below the mean value for a normal population defined a “hypocontractile segment.” The “percent hypocontractile perimeter” was defined as the length of the hypocontractile segment divided by the total ventricular perimeter excluding the aortic and mitral valves. Examples of the left ventriculograms obtained before and during balloon inflation in two patients are shown in figure 3 and 4.

Study protocol

Cyclo O, baseline before PTCA. A 12-lead electrocardiogram was obtained, followed by arteriograms of the contralateral artery using the No. 5F coronary catheter. Injection of the contralateral artery allowed assessment of the degree of collateral filling before dilatation. Thereafter the No. 5F pigtail was
advanced to the left ventricle, pressures were recorded, and a left ventriculogram in the 20 degree right anterior oblique view was obtained by digital subtraction techniques. After the pigtail catheter was withdrawn to the descending aorta, multiple views of the stenosed vessel being dilated were obtained through the Stertzer guiding catheter and the deflated angioplasty balloon was guided through the lesion. Routine PTCA proceeded with two inflations. Just before deflating the balloon during the second inflation, an injection was made through the guiding catheter to document the absence of any flow around the inflated balloon and the absence of any intracoronary collateral filling. Several minutes after recovery from these initial inflations three additional inflations were performed during which the “study” variables were measured.

**Cycle 1.** The pigtail catheter was advanced into the left ventricle. Immediately before and throughout balloon inflation simultaneous aortic and left ventricular pressure were continuously recorded as well as a rhythm strip. At 30 sec into balloon inflation, a simultaneous 12-lead electrocardiogram was recorded. At 40 sec the inflation was terminated.

**Cycle 2.** Pressures were continuously recorded before and during TCA. The pigtail catheter was advanced into the left ventricle. Immediately before and throughout balloon inflation simultaneous aortic and left ventricular pressure were continuously recorded as well as a rhythm strip. At 30 sec into balloon inflation, a simultaneous 12-lead electrocardiogram was recorded. At 40 sec the inflation was terminated.

**FIGURE 1.** Assessment of collateral filling in patient 1. A. Before angioplasty (Pre TCA), there is a 90% stenosis in the mid left anterior descending artery (LAD). B. There are no visible collaterals (coll grade = 0) originating from the right coronary artery (RCA). C. During balloon inflation, no visible collaterals (coll grade = 0) are seen originating from the RCA.

**FIGURE 2.** Assessment of collateral filling in patient 3. A. Before angioplasty there is a 90% stenosis in the mid left anterior descending artery (LAD). B. There are no visible collaterals (coll grade = 0) originating from the right coronary artery (RCA), even late after the injection when the myocardial blush appears. C. During balloon inflation, multiple collateral (coll) channels are seen originating from the RCA, which completely fill (coll grade = 3) the epicardial segment of the mid and distal LAD.
FIGURE 3. Cycle 0 (A) and cycle 2 (B) left ventriculograms for patient 1. In comparison to the normal left ventriculogram before PTCA, the ventriculogram during balloon inflation reveals hypocontractility involving 31% of the left ventricular perimeter (%HYP = 31).

Throughout balloon inflation as well as a rhythm strip. At 30 sec into balloon inflation a simultaneous 12-lead electrocardiogram was recorded. At 40 sec a left ventriculogram was acquired, and the balloon was immediately deflated.

Cycle 3. The pigtail catheter was removed and a No. 5F arteriography catheter was placed in the contralateral artery. At 30 sec into balloon inflation a simultaneous 12-lead electrocardiogram was repeated. At 40 sec an arteriogram of the contralateral artery was obtained.

Cycle 4. After removing the balloon catheter, a final injection of the contralateral artery was made.

Three minutes of recovery with the balloon deflated was allowed between each inflation cycle. The hemodynamic measurements recorded for analysis were those measured at 35 sec into inflation.

Statistics. All continuous variables are presented as the mean ± SD. The examination of the differences between the control cycle (0) and the intervention cycles (2 and 3) involved one-way analysis of variance and the paired t test. The nonparametric statistic, the Spearman rank correlation coefficient, was used to test the relationship between collateral grade (measured on an ordinal scale of 0 to 3) and the variables measuring the extent of myocardial ischemia.

Results

Changes in collateral filling during coronary occlusion (figure 5). Baseline arteriography of the contralateral vessels immediately before passage of the angioplasty balloon revealed a mean grade of collateral filling of 0.5 ± 0.8. During balloon inflation, there was a significant increase in the mean grade of collateral filling to 1.7 ± 1.0 (p < .01). Nineteen of the 23 patients had an improvement in collateral filling by at least one grade. Seven of the 23 patients had an improvement of at least two grades. Six patients with no visible collaterals originally had an increase in collateral filling to grade 2 or 3. Arteriography, after the stenosis was dilated and the balloon catheter removed, revealed no visible collateral channels to the dilated vessel in any patient.

Hemodynamics. No significant changes were observed in heart rate, mean aortic pressure, or the product of heart rate and peak systolic aortic pressure. Heart rate increased slightly from a mean of 76 ± 14 (cycle 0) to 79 ± 10 and 78 ± 11 beats/min (cycle 2

FIGURE 4. Cycle 0 (A) and cycle 2 (B) left ventriculograms for patient 3. In comparison to the normal left ventriculogram before PTCA (%Hyp = 0), the ventriculogram during balloon inflation reveals hypocontractility involving 10% of the left ventricular perimeter (%HYP = 10).
and 3) \( (p = \text{NS}) \). The mean aortic pressure decreased slightly from 88.6 ± 8.7 (cycle 0) to 87.5 ± 4.5 and 85 ± 13 mm Hg (cycles 2 and 3) \( (p = \text{NS}) \). The heart rate–aortic systolic pressure product was unchanged from 8744 ± 1538 to 8702 ± 1338 (cycle 0 vs 2). In contrast, left ventricular end-diastolic pressure increased slightly but significantly, from 11.3 ± 2.8 (cycle 0) to 13.7 ± 4.2 and 14.0 ± 3.4 mm Hg (cycles 2 and 3) \( (p = .04) \).

**Indexes of myocardial ischemia with reference to collateral filling** (table 2). Sudden coronary occlusion by the angioplasty balloon resulted in significant myocardial ischemia as assessed by the sum of ST segment elevation and by the percent hypocontractile perimeter. Nineteen of 23 patients developed new ST segment elevation greater than 0.5 mm as compared with their baseline electrocardiogram. One patient developed isolated ST segment depression and the remaining three patients had no electrocardiographic changes at 30 sec into inflation. There was a weak association between the sum of ST segment elevation and the grade of collateral filling during cycle 0 \( (r = -.40) \). However, a highly significant correlation was observed between the sum of ST segment elevation during balloon inflation (cycle 2) and the grade of collateral filling during inflation cycle 3 \( (r = -.87) \) (figure 6).

New wall motion abnormalities were observed during the cycle 2 left ventriculogram in 19 of 23 patients. The wall motion ranged from 5% to 40% of the left ventricular perimeter. Three patients had no new wall

![Figure 5](https://example.com/figure5.png)

**FIGURE 5.** Change in grade of collateral filling arising from the contralateral coronary artery before, during, and after balloon occlusion (cycles 0, 3, and 4) of the stenosed coronary artery in 23 patients.

abnormalities. There was a weak association between the percent hypocontractile perimeter and the grade of collateral filling during cycle 0 \( (r = -.50) \). However, a highly significant correlation was observed between the percent hypocontractile perimeter assessed during cycle 2, and the grade of collateral filling assessed during cycle 3 \( (r = -.85) \) (figure 7).

Fourteen of the 23 patients developed typical anginal pain during each balloon inflation (table 3). The time of onset of pain ranged from 24 sec to 40 sec after the beginning of the balloon inflation. Nine of the 23 patients experienced no angina during the inflation cycles. All nine patients had either grade 2 or 3 collaterals. All of the patients with only grade 0 or 1 collaterals experienced angina within 40 sec.

**Discussion**

Our study constitutes the first prospective analysis of the functional significance of the coronary collateral circulation in a large group of patients with fixed, severe atherosclerotic heart disease. With the angioplasty procedure described above, major study variables derived from the prior history, physical, laboratory, and angiographic examinations were identified before as well as during the controlled coronary artery occlusions. In addition, we selected patients in whom no other stimuli to collateral flow other than fixed coronary obstruction were apparent. In a similar study population with the same entry criteria, we previously reported that in a high percentage of patients with severe coronary stenosis, collateral channel filling was augmented to a higher grade within 60 to 90 sec after balloon occlusion. In the present study we attempted to assess the functional significance of these acutely expanded collateral channels.

**Previous studies of collaterals in chronic ischemic heart disease.** The earliest studies applied intracoronary injection techniques during the pathologic evaluation of postmortem hearts. Using these techniques, Blumgart et al. and Baroldi observed that a significant number of patients who had sustained total coronary occlusion had large interarterial anastomotic channels that filled the blocked coronary arteries retrogradely. In spite of the total obstructions, however, many of these patients had no evidence of ischemic injury. These investigators suggested that the collateral flow passing through the interarterial anastomoses protected the jeopardized zone. Later, investigators applied selective coronary arteriography in vivo and observed major intercoronary and intracoronary collateral channels filling vessels retrogradely. Using these techniques, Helfant et al. suggested that there were no significant differences
TABLE 2
Individual patient characteristics in relation to the change in collateral filling

<table>
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<tr>
<th>Patient</th>
<th>Collaterals Before PTCA</th>
<th>Collaterals During PTCA</th>
<th>Vessel dilated</th>
<th>Heart rate (beats/min) Before PTCA</th>
<th>Heart rate (beats/min) During PTCA</th>
<th>Ao systolic (mm Hg) Before PTCA</th>
<th>Ao systolic (mm Hg) During PTCA</th>
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Ao systolic = systolic aortic pressure; %Hyp = percentage of the left ventricular perimeter that became hypococontractile; LVEDP = left ventricular end-diastolic pressure.

*During PTCA.

between patients with those without collaterals with regard to the extent of ventricular asynergy or hemodynamic indexes of left ventricular dysfunction. However, they did observe a trend toward lower mortality during the follow-up period. In contrast, Levin et al. and Webster et al. studied patients with total occlusion of at least one coronary artery, and both investigators concluded that patients with collaterals had better ventricular function than patients who progressed to total occlusion in the absence of collaterals. More recently, the impact of collateral circulation has been assessed during the acute phase of myocardial infarction. Although several of these studies suggested that collaterals in the early hours of acute infarction were associated with relatively smaller infarcts, these studies were limited by the fact that the patients presented several hours after total occlusion of the infarct-related artery, very little information was available regarding the clinical and coronary arteriographic characteristics of the patients before infarction, and additional therapeutic interventions were often employed that may have also limited infarct size.

Collaterals in coronary spasm. The first prospective assessment of changes in collateral circulation during sudden reduction of coronary blood flow was undertaken in patients with coronary spasm by Takeshita et al. and Tada et al. Ergonovine was administered and immediately after the onset of coronary spasm, the contralateral artery was injected. In some patients, collateral filling of the spastic artery was observed that was not present angiographically prior injections when the native coronary arteries were not in spasm. These patients with good collateral filling of the artery induced to spasm had only ST segment depression and not the ST segment elevation expected after sudden transmural ischemia. Tada suggested that collateral flow could have a role in preventing transmural ischemia, but no ventriculographic studies were performed during coronary spasm to prove the hypothesis.

**Present study.** The data presented in this study, comparing ventriculographic findings during sudden coronary occlusion with the degree of collateral filling seen during occlusion, strongly suggest that the coronary collateral circulation does limit myocardial ischemia in man. This protective role was apparent in our model of transient, sudden, and total coronary occlusion. The
protection afforded does not appear to be an all-or-none phenomenon but rather a graduated one. In general terms, grade 0 or 1 collateral filling can be viewed as conferring a negligible degree of protection. All three indexes of myocardial ischemia (percent hypocontractile perimeter, sum of ST segment elevation, and onset of angina) were markedly positive in all patients with only grade 0 or 1 collateral filling. Although earlier anatomic investigations demonstrated that narrow intercoronary collateral channels between 100 to 300 μm in diameter are congenitally present in normal hearts,20,21 our data suggest that these small collateral channels are not large enough to protect myocardium in jeopardy. In contrast, grade 2 collaterals confer an intermediate degree of myocardial protection. Although there was a greater variability with respect to the percent hypocontractile perimeter in patients with grade 2 collateral filling as compared with grade 0 or 3, the majority of patients with grade 2 collaterals demonstrated new zones of asynergy that were intermediate in size compared with those of patients with either grade 0 or 3 collaterals. Grade 3 collaterals appear to be almost completely protective. The only patients without any new asynergy during coronary occlusion were those with grade 3 collaterals.

The tendency toward greater protection with higher collateral grade applied to patients with left coronary as well as right coronary artery occlusion, and also to proximal as well as distal coronary artery occlusion.

Limitations of the study. First, all patients received the vasodilators nitroglycerin and nifedipine. Recent work by Bass et al.22 suggested that nitroglycerin did not have a significant impact on collateral filling. Furthermore, all patients received the same dose of nifedipine and did not sustain any major drops in aortic pressure between the different study cycles. Therefore it is unlikely that the vasodilators we gave had a significant effect on our observations.22 Second, we did not evaluate absolute flow through the collateral channels. In lieu of flow, we applied a grading scale for collateral filling that was developed and validated13 without any knowledge of the subsequent outcome on left ventricular function of sudden coronary occlusion. Third, al-
though our evaluation suggests that collaterals are protective during the first minute of coronary occlusion, their impact after several hours remains to be determined.

Clinical implications. First, our observations suggesting greater myocardial protection with higher collateral grade may in part explain the variable infarct size observed in patients with coronary occlusions in similar anatomic locations. Second, proof of the protective effect of collateral filling provides impetus for studying markers of collateral reserve and testing therapeutic modalities that may augment collateral filling.

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