

Temporal Evolution of the Human Coronary Collateral Circulation After Myocardial Infarction

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An analysis of the coronary collateral circulation in a consecutive series of 116 postinfarction angiograms from patients with persistent 100% occlusion of their infarct artery is reported. Patients were classified into four groups according to the interval between acute infarction and angiography. Of 42 patients studied within 6 hours of infarction (Group I), 52% had no evidence of any coronary collateral development as compared with only 8% (1 of 16 patients) studied 1 day to 2 weeks after infarction (Group II). Virtually all patients studied beyond 2 weeks after myocardial infarction (14 to 45 days, Group III) and later than 45 days (Group IV) had visible collateral flow. Angiographically "well developed" collateral channels were seen in only 16% of Group I patients compared with 62, 75 and 84% of patients in Groups II to IV, respectively. Of six patients studied twice, on the

day of the infarction and 2 weeks later, only one patient had collateral vessels on the day of infarction, whereas all six patients did at follow-up study. Group I patients were studied as part of a randomized acute myocardial infarction reperfusion trial, whereas the other patients were referred for angiography primarily because of post-infarction ischemia.

Within the limitations imposed by the patient selection process, it is concluded that well developed coronary collateral vessels are rarely present at the time of infarction. After infarction, they develop rapidly and are generally demonstrable within 2 weeks. It may also be inferred that the preservation of ischemic myocardium by well developed coronary collateral vessels at the time of myocardial infarction may be an uncommon occurrence.

The role of human coronary collateral circulation in protecting myocardium jeopardized by the occlusion of its primary vessel has been debated for most of this century (1-7). Although early pathologic studies (8-11) speculated that the presence of collateral vessels limited the size of myocardial infarction, other investigations (12,13) failed to corroborate these findings. Thus, despite ever increasing interest, the protective role of the collateral circulation in patients experiencing myocardial infarction remains to be defined.

The uncertainties are in a large part due to the inherent difficulties in the study of this issue (4,14,15). Investigators limited to the use of postevent (that is, well after myocardial infarction) angiographic and pathologic evaluation of collateral vessels have assumed that their observations reflected conditions at the time of coronary occlusion. This assump-

tion fails to take into account the dynamic development, growth and regression of the human coronary collateral circulation.

Recent efforts to reperfuse coronary arteries in patients with acute myocardial infarction (16-20) have for the first time enabled us to systematically evaluate coronary collateral vessels at the time of coronary occlusion. In addition to supplying this new vantage point, such interventions have further heightened interest in the possibility that collateral vessels play a significant role in promoting beneficial outcome after successful thrombolysis. Therefore, we undertook a study to define the incidence and rate of development of coronary collateral vessels in patients after myocardial infarction.

Methods

Study patients. A consecutive series of 116 angiograms from 110 patients with documented myocardial infarction and persistent 100% occlusion of the artery supplying the infarcted area ("infarct artery") at the time of angiography were analyzed for coronary collateral status. The patients

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were classified into four groups according to the time between myocardial infarction and angiography as follows (Table 1): Group I consisted of 42 patients studied on the day of infarction as part of a coronary reperfusion trial. The mean interval between symptoms and angiography was 4 hours and 10 minutes. Group II represented 13 patients with infarction more than 1 day but less than 2 weeks before angiography, and included the follow-up study of 6 patients from Group I. Group III consisted of 16 patients studied between 14 and 45 days after acute infarction and Group IV comprised 45 patients studied more than 45 days after infarction.

Entrance criteria were that myocardial infarction be documented by angiographic segmental wall motion abnormality plus history, electrocardiographic or serum enzyme changes compatible with acute infarction. In addition, patients in Group I had to meet entrance criteria to our reperfusion protocol which required chest pain of at least 30 minutes' duration (unresponsive to nitroglycerin) and electrocardiographic changes consisting of 2 mm of ST segment elevation in at least two contiguous leads with or without evolving Q waves. Despite these additional entrance criteria for Group I patients, the clinical histories of the different groups were very similar. The index infarction was the first myocardial infarction in almost all (88%) of the patients studied. Prior infarction was equally distributed among the subgroups. Chronic angina pectoris was reported to have preceded infarction in approximately half of the patients and in a similar proportion for each group (Group I 57%, Group II 50%, Group III 71%, Group IV 45%).

All 42 patients in Group I were subsequently documented to have acute myocardial infarction by serum enzyme determination. Determination of collateral status for Group I patients was made from the initial selective angiogram of the "noninfarct vessel" and then of the infarct artery when first identified as 100% occluded, that is, before administration of thrombolytic therapy.

Exclusionary criteria for Group I were: age older than 75 years, bleeding disorder, recent surgery, history of peptic ulcer disease or history of cerebrovascular disease. Patients with significant valvular disease or previous coronary artery bypass graft surgery were also excluded from the study.

Table 1. Distribution of 116 Postinfarction Angiograms From 110 Patients With Persistent Total Occlusion of the "Infarct Artery"

Group	Interval From Infarction to Angiography	No. of Cases
I	1 to 6 hours	42
II	2 to 13 days	13
III	14 to 45 days	16
IV	>45 days	45

Coronary arteriography. All patients underwent selective coronary angiography in multiple projections using the femoral artery approach. Group I patients had the non-infarct vessel studied first.

Collateral vessels were scored by two independent observers according to the degree of opacification of the native vessel distal to its occlusion. Collateral vessels were assigned a numeric score between 0 and 3 according to the following scheme (Fig. 1):

- 0 = no angiographic filling of the infarct vessel distal to occlusion,
- 1 = faint opacification of the distal vessel or only small fragments of the distal vessel visualized,
- 2 = visualization of a long segment (greater than half of the estimated length) of the distal vessel though less well opacified than a normal vessel of equal caliber, and
- 3 = entire distal vessel well visualized and densely opacified.

When the degree of opacification varied in a given study, the score corresponding to the best visualization of the distal vessel was used. In cases where the distal segment of the occluded vessel filled from both right and left coronary collateral vessels, the sum of the scores (not to exceed 3) was used. Scoring differences between the two observers of one grade or less were averaged, while differences greater than one grade were adjudicated by a third independent observer. This scoring system did not grade the collateral conduit itself, but rather the angiographic result of its presence as demonstrated by the distal filling of a completely occluded artery. Furthermore, time required for opacification through collateral channels was not considered in this scoring system.

Data analysis. All values are presented as mean \pm standard error of the mean. Statistical analyses of collateral scores were performed with the use of Student's *t* test. Frequency analysis examining differences between groups was performed by Fisher's exact test. A probability (*p*) value of less than 0.05 was considered to be significant.

Results

Distribution of coronary collateral scores by group. Of the 42 patients in Group I, 22 (52%) had no evidence of collateral vessels (score = 0) and 11 (26%) had poor collateral development (score > 0 to 1.0). Seven patients (17%) had fair collateral development (score > 1.0 to 2.0) and only two patients (5%) had well demonstrated collateral filling (score > 2) (Fig. 2).

Of the 13 Group II patients studied between 1 and 13 days after myocardial infarction, 1 patient (8%) had no

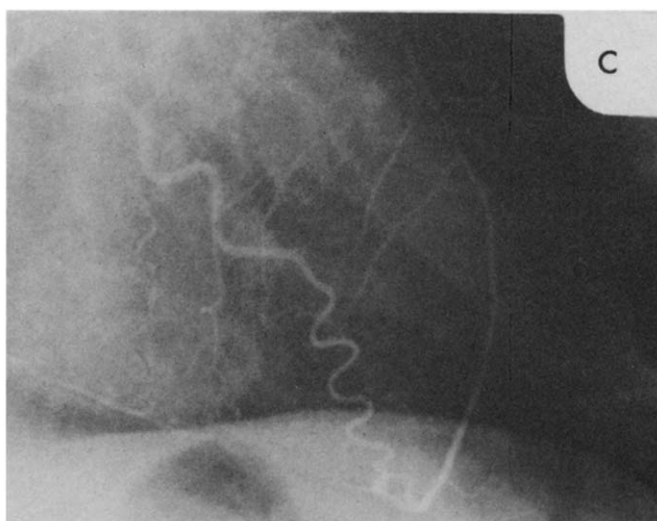


Figure 1. Examples of coronary collateral vessels filling an occluded left anterior descending artery in three patients. Coronary collateral scores were: A = 1, B = 2 and C = 3.

collateral vessels, 4 (31%) had poor, 3 (23%) had fair and 5 (38%) had good collateral function.

In Group III, studied 14 to 45 days after myocardial infarction, all 16 patients had some evidence of collateral development. Three patients (19%) had poor, four (25%) had fair and nine (56%) had good coronary collateral function.

Of the 45 patients studied 45 days after myocardial infarction (Group IV), only 1 patient (2%) had no collateral vessels while 5 (11%) had poor, 13 (29%) had fair and 26 (58%) had good collateral function.

By combining scores of 2 or greater, the percent of patients with "well developed" coronary collateral vessels in each group was 16, 62, 75 and 84% (Groups I to IV, respectively) (Fig. 3). Group I was significantly different from

Groups II, III and IV ($p < 0.001$), while Groups II, III and IV were not significantly different from each other.

Comparison of mean collateral scores of the four groups serves to further demonstrate the relation between collateral development and time (Table 2). The mean collateral score \pm standard error of the mean was 0.6 ± 0.1 for Group I, 1.8 ± 0.3 for Group II, 2.3 ± 0.2 for Group III and 2.4 ± 0.1 for Group IV. Group I was significantly different from Groups II, III and IV ($p < 0.001$), while no statistically significant difference was found among Groups II, III and IV.

Sequential coronary collateral determination. Six patients from Group I were restudied 10 to 14 days after myocardial infarction as per our reperfusion protocol. On initial angiography, only one of the six patients had any evidence of collateral vessels (score 0.5, mean score for the six patients 0.1). However, at follow-up study, all six patients had evidence of some collateral function (mean score 1.1) ($p < 0.05$)

Discussion

The functional significance of the human coronary collateral circulation has been controversial since its description by Richard Lower in 1669 (21). Among the most important issues surrounding these vessels has been their ability to prevent or limit the consequences of acute myocardial infarction. Numerous studies in animals (22-27) have demonstrated that experimentally induced gradual coronary occlusion, allowing time for the development of collateral vessels, is associated with prevention or limitation of the size of resulting myocardial infarction. However, results of investigations in human patients have been less conclusive.

The landmark pathologic study of Blumgart et al. (8) in 1940 concluded that with the presence of collateral vessels,

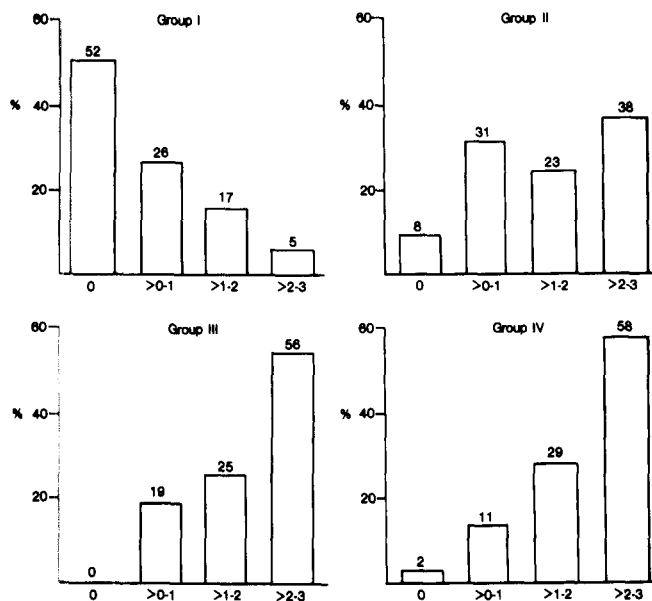


Figure 2. Distribution of coronary collateral scores of Groups I to IV. The numbers on the top of the bars represent percent of patients.

major human coronary arteries may be occluded without resultant myocardial damage. This important function of human coronary collateral vessels was questioned in 1955 when Snow et al. (13) repeated the work of Blumgart et al. and found that collateral vessels rarely prevented myocardial infarction when coronary arteries became occluded. Although they demonstrated that collateral vessels may have a role in limiting the extent of necrosis, the controversy over the importance of these vessels grew.

Angiographic assessment of coronary collateral vessels. Our information in this regard increased dramatically, if not definitely, with the clinical introduction of selective

Figure 3. Percent of patients in each group with coronary collateral scores of 2 or greater. The numbers on the top of the bars represent percent of patients in each group achieving a score of 2 or greater. * = $p < 0.001$ for Group I versus Group II, III or IV.

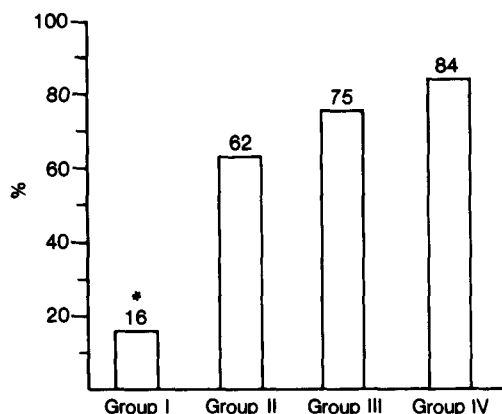


Table 2. Coronary Collateral Circulation Scores

Group	Mean Score \pm SEM
I	0.6 \pm 0.1*
II	1.8 \pm 0.3
III	2.3 \pm 0.2
IV	2.4 \pm 0.1

* $p < 0.001$ for Group I versus Group II, III or IV.

coronary angiography in the 1960s. Case reports of total coronary occlusion (28,29) (even of the left main artery [30]) with normal left ventricular function were soon confirmed by studies (4,7,15) reporting the incidence of this association to be 28 to 44%. Despite this incontrovertible evidence of the protective effects of collateral vessels, numerous investigations (2,3,5,31) concluded that the frequency and size of myocardial infarction were not influenced by the presence of these vessels.

The cause of these conflicting conclusions and the controversy that has ensued can be traced to the inherent methodologic difficulties in the study of the human coronary collateral circulation, that is, the quantitation of collateral flow, the variable definition of significant stenosis resulting in differing study populations and the inability to retrospectively know whether the collateral vessels observed in a patient after myocardial infarction were present at the critical hour of coronary occlusion.

The relevance of the first two difficulties was recently reviewed (14,15) and will only be briefly discussed here. As yet, no satisfactory method of quantitating collateral flow has been devised. Although coronary angiography is most frequently employed, it is with the understanding that current angiographic technique affords, at best, a crude estimation of collateral flow. In addition to its limited resolution of 100 μ , which ignores smaller collateral channels (which can be as small as 40 μ), differences in angiographic technique and grading systems make conclusions from different studies difficult to compare. The problems resulting from various definitions of coronary artery disease have been pointed out by Levin et al. (4). Although it is now generally accepted that collateral conduits are rarely present in vessels with less than 90% narrowing, several investigators studying the impact of collateral vessels in patients with coronary artery disease have included patients with 75% stenoses. Defining coronary disease as the presence of 75% or greater stenosis allows patients with noncritical stenosis (that is, lesions of insufficient hemodynamic significance to promote collateral development) to be included in the study group. As a result, previously reported patient groups with collateral vessels tend to have more severe coronary artery disease than do comparison groups without collateral vessels.

To minimize the impact of these two factors in our study, a simple, easily corroborated collateral scoring system was used in patients with 100% occlusion of the infarct artery.

Previously, all human studies attempting to determine the role of coronary collateral vessels in patients with acute myocardial infarction were performed at a time remote from the acute event. The interpretation of such studies required the extrapolation of the observed status of collateral circulation to that at the time of coronary occlusion. To do this, a time frame for human collateral development had to be estimated.

Rate of coronary collateral development. Although the temporal evolution of collateral development in several experimental models was fairly well established (6,32-34), the absence of a model truly applicable to patients with coronary artery disease plus the absence of direct clinical observations made this estimation extremely difficult. Anecdotal reports of patients with normal coronary arteries that had angiographically demonstrable functioning collateral networks (35,36) were balanced by clinical (pathologic and historic) studies which estimated that a period of 8 weeks after myocardial infarction (21) or a period of 3 months of angina (37) was a requisite for collateral development.

The recent trend toward early intervention in patients with acute myocardial infarction has afforded us the opportunity to observe the status of coronary collateral vessels at the time of coronary occlusion. Along with this new vantage point has come heightened interest in the relation between collateral vessels and acute myocardial infarction; it has been suggested that the presence of collateral vessels may play an important role in sustaining jeopardized myocardium until reperfusion can be accomplished. To define the extent of collateral circulation at the time of acute myocardial infarction and to estimate the subsequent temporal evolution of these vessels, we analyzed the collateral development of 42 patients studied within 6 hours of acute infarction and a consecutive series of 74 patients with well demonstrated myocardial infarction studied at a time remote from the event.

Our results show that the incidence of patients with well developed coronary collateral vessels in the first few hours after clinical infarction is disappointingly small (Fig. 2). Collateral circulation scores of greater than 2 were only present in 5% of this group (Group I), while 78% had scores of 1 or less. This paucity of collateral vessels was not observed in the group studied as soon as 1 to 13 days after myocardial infarction (Group II), and there was a further gradual tendency toward higher collateral scores as the interval between infarction and angiography increased. The mean collateral scores of the four groups (Table 2) and the percent of patients in each group with high grade collateral vessels (Fig. 3) demonstrated the relation between coronary development and time.

The relative absence of coronary collateral vessels early in the infarct course and their subsequent rapid development were further illustrated by a group of six patients whose total occlusion was initially relieved, but whose follow-up

angiogram performed 10 to 14 days after infarction demonstrated reocclusion of the infarct artery. Whereas acutely only one patient had any evidence of coronary collateral vessels, by 2 weeks all six patients demonstrated collateral development.

Our results are in good general agreement with other recent data from patients experiencing acute myocardial infarction. The reported incidence of coronary collateral vessels in acute myocardial infarction intervention trials (16-20) has varied from 15 to 53%. This wide range is not surprising given the differences in study groups as well as the general lack of definition of what was considered a collateral vessel. While all of these referenced studies evaluated patients "acutely," the definition of acute ranged from 3 to 24 hours. In our study, all Group I patients were evaluated within 6 hours of the onset of symptoms.

Limitations. Although the grading system for collateral circulation employed in this study was internally reproducible, it was nonetheless subjective and only semiquantitative. Our study design was such that we have no data relating the angiographic appearance of collateral vessels and ventricular functional performance outcome. The assumption that very poor visualization of collateral filling is physiologically different from dense opacification remains to be resolved, although a correlation has been reported (38) between the angiographic grading of coronary collateral circulation (according to the number of collateral vessels visualized and their density of opacification) and the intraoperative measurement of retrograde flow. Further, although the patients in our study represent a consecutive series of patients undergoing angiography after myocardial infarction, certain limitations inherent in this method of patient selection deserve discussion. Our patients studied within 6 hours of symptom onset represent a very selected subgroup with particularly unequivocal infarct presentation. It remains possible, therefore, that other patients with infarction with less severe pain or more equivocal electrocardiographic findings on hospital arrival might show a different (higher) frequency of early collateral development. Patients included as representative of late postinfarction survivors were biased toward those with recurrent ischemia since this was the usual indication for angiography. Optimally, serial angiograms in a single study group would be more definitive in documenting the rate of coronary collateral growth, but we were only able to obtain such studies in a small subgroup (six patients). Finally, because this analysis is retrospective, no standard medical regimen (for example, nitrates) that could conceivably influence collateral visualization was applied.

Conclusions. The angiographic analysis of the coronary circulation of a consecutive series of 116 angiograms from 110 patients with myocardial infarction and persistent 100% occlusion of the infarct artery is reported. In the group of patients with acute myocardial infarction, as defined by our reperfusion protocol, well developed coronary collateral

vessels are rarely present at the time of myocardial infarction. After coronary occlusion, collateral vessels develop rapidly and are generally demonstrable within 2 weeks. Thus the angiographic demonstration of coronary collateral circulation at any time later than the day of infarction does not imply that collateral vessels were present at the time of coronary occlusion. Furthermore, the preservation of ischemic myocardium by well developed collateral vessels at the time of myocardial infarction may be an infrequent occurrence.

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