Recent Insights Into Coronary Collateral Circulation

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The coronary collateral circulation is an alternative source of blood supply to the myocardium jeopardized by failure of the original vessel to provide adequate flow to the major epicardial branches of the coronary artery. There has been considerable debate, however, concerning the functional role of collaterals in humans. Extensive studies carried out in the past several years in experimental animals, in autopsy materials, or in intact human hearts have confirmed the substantial potential of collaterals in limiting the extent of myocardial ischemia, preventing cell death, and altering the clinical outcome of ischemic heart disease, although these effects depend largely on the rate at which the collateral circulation develops and the magnitude of flow permitted by the newly recruited vessels.

Previously, there were considerable limitations in the assessment of collaterals early after the onset of myocardial infarction. With the advent of direct reperfusion through angiographic techniques during the acute stage, however, a unique opportunity for prospective evaluation of the functional significance of collateral circulation in the setting of sudden coronary occlusion has been provided. A useful animal model of collateral development without persistent coronary stenosis has now been established and has permitted more systematic analysis of collateral formation and function. Assessment of the mechanisms of neovascularization and regulation of endothelial cell growth have been facilitated by the establishment of large-vessel endothelial cells in culture and identification of angiogenic factors.

This brief review summarizes the current knowledge of collateral formation and function and describes a potential therapeutic modality by which the factors promoting collateral development might benefit patients with coronary artery disease.

Functional Significance of Collateral Circulation

Earlier studies performed in postmortem hearts to correlate the extent of collateral network with clinical findings during life demonstrated that collaterals were better developed in patients with longer duration of ischemic symptoms and/or with more severe coronary arterial narrowing.

More recently, coronary arteriography has permitted correlation of the anatomic appearance of coronary collateral vessels with the underlying coronary artery disease. In particular, coronary thrombolysis performed during the first few hours of acute myocardial infarction provided a unique opportunity to evaluate the role of coronary collaterals in minimizing myocardial infarct size. A number of studies suggest that among patients with acute myocardial infarction and unsuccessful intracoronary thrombolytic therapy early after onset of symptoms, subsequent improvement in global function and wall motion in the infarct zone frequently can be expected where residual flow was maintained by extensive collaterals to the region perfused by the infarct-related vessel.

We have previously demonstrated that collaterals are a key determinant of the creatine kinase time–activity curve. In patients in whom thrombolysis was unsuccessful but collateral channels are angiographically demonstrable, peak creatine kinase level was attained earlier than in patients without visible collaterals in the absence of recanalization. Thus, collaterals definitely provide significant blood supply to the myocardium at risk (Figure 1). The recent larger-scale trial of coronary thrombolysis reported by Habib et al offered additional confirmation of these observations by showing that in patients who failed to reperfuse, the presence of angiographically documented collaterals in the initial hours of acute myocardial infarction was accompanied by significantly lower serum creatine kinase levels and hence limitation of enzymatic estimates of infarct size. Also, in a subgroup, patients with collaterals had higher ejection fractions than those without collaterals before discharge.

A protective effect of coronary collaterals in acute myocardial infarction in humans has also been evidenced by protection against left ventricular aneurysm formation in patients with unsuccessful reperfusion. Recently, we assessed the relation of the coronary collateral circulation to regional myocardial function and later formation of ventricular aneurysm in 47 patients with a first acute anterior myocardial infarction. All of these patients had a complete occlusion of the proximal part of the left anterior descending coronary artery and were treated with intracoronary thrombolysis during the first 6 hours after the onset of symptoms. In 25 patients, thrombolysis was successful; in 10 patients, reperfusion was unsuccessful with collaterals present; and in 12 patients, reperfusion was un-
successful in the absence of significant collateral perfusion. In the chronic phase, further improvement of ventricular function was observed in the former two groups but not in the latter group with absence of reperfusion and no collaterals. Even when the reperfusion attempt failed, the incidence of aneurysm formation was considerably lower in patients with a significant collateral circulation (10% versus 58%) (Figure 2).

Forman et al. also observed that total occlusion of the left anterior descending coronary artery in association with poor collateral blood supply predisposes to left ventricular aneurysm formation after anterior myocardial infarction.

Pick and Becker evaluated the collateral circulation in human myocardium by combining postmortem coronary angiography with the injection of radioactive microspheres and histological examination. They demonstrated that the variations in infarct size result primarily from variations of transmural extent of infarction, which was directly related to the extent of the collateral networks. Alterations in left ventricular volumes after a first acute transmural infarction were shown to be closely related to the residual flow either by spontaneous reperfusion of the infarct-related arteries or by collateral vessels that prevent left ventricular enlargement and functional deterioration. In experimental studies, it was shown that late reperfusion failed to reduce infarct size or prevent ventricular dilatation but still contributed to inhibit infarct expansion and enhance scar thickening. The thick scar could reduce passive expansion of the ischemic myocardium during systole and decrease oxygen demand through the Laplace principle. Thus, coronary collaterals may prevent left ventricular aneurysm formation by limiting the extension of the wave front of necrosis from the subendocardial to subepicardial layers or by improving healing of the infarcted tissue and diminishing infarct expansion.

All of these data substantiate the importance of residual blood supply to the infarcted myocardium and offer strong evidence that coronary collaterals do indeed limit ischemic injury.

**Stimulation of Collateral Development**

**Collateral Recruitment**

Collateral blood flow increases gradually until 24 hours after the production of myocardial ischemia by an abrupt occlusion of the coronary artery. Judgutt and coworkers demonstrated in conscious dogs that intravenous nitroglycerin increased collateral flow, with subsequent reduction in infarct size after permanent coronary occlusion in the setting of mild hypotension and no sustained reflex tachycardia. They suggested that myocardial protection by nitroglycerin is mediated largely by a direct vasodilating effect on the coronary bed rather
than a decrease in myocardial oxygen demands. Subsequently, they extended this result in a clinical setting and demonstrated that low-dose intravenous nitroglycerin therapy during acute myocardial infarction salvaged myocardium and limited infarct expansion by collateral recruitment.36

It has also been demonstrated that repetitive brief coronary occlusions produce a progressive augmentation in native collateral flow.22,37 Recently, we emphasized the importance of myocardial ischemia for this recruitment of a native collateral circulation.38 We designed three different coronary occlusion protocols in anesthetized open-chest dogs with various durations of each occlusion and the same total occlusion time: 1) 30 10-second left anterior descending coronary artery occlusions at 1-minute intervals, 2) five 1-minute coronary occlusions at 1-minute intervals, and 3) one 5-minute continuous occlusion. Each procedure provided a total of 300 seconds of pressure gradient across the collateral network but different severities of myocardial ischemia because the pressure gradient between the donor and recipient coronary arteries can be established in a few seconds after coronary occlusion,39 whereas a longer time is necessary for the myocardium to be rendered fully ischemic.40,41 In this study, the collateral blood flow from the circumflex artery to the area perfused by the anterior descending artery was measured as a stepwise decrease in circumflex flow upon the release of the left anterior descending artery occlusion. This test is considered to reflect the prompt reestablishment of antegrade anterior descending artery flow with elimination of circumflex to anterior descending artery pressure gradient.42 The collateral flow estimated from this stepwise reduction in the left circumflex coronary artery flow was 1.6 ml/min at 10-second test occlusion in the baseline state. Thirty 10-second occlusions did not affect this flow, whereas after five 1-minute occlusions and one 5-minute occlusion, this collateral flow was increased to 3.0 and 3.5 ml/min, respectively.43 The delayed response of the collateral circulation to myocardial ischemia may be explained, at least in part, by the location of collateral vessels. Because in the canine heart the collaterals exist in the subepicardial layer,43 it may take longer for adenosine accumulated in the myocardium to dilate the collateral channels.44 Alternatively, flow-dependent collateral dilatation may account for the progressive increase in collateral flow after the establishment of a pressure gradient across the collateral network.45 Although it is difficult to extrapolate these experimental observations directly to humans, the information has greatly helped our understanding of the role of coronary collaterals.

Clinically, delayed collateral opening may in part explain walk-through angina46 and diurnal variations in myocardial ischemic threshold47 in patients with a significant collateral circulation. In 10 patients with well-developed collateral circulation, the extent of ST depression at 3 minutes of bicycle exercise with fixed work load was 0.20 mV, but this depression was significantly reduced to 0.16 mV at the end of exercise when the double product was 9% greater than that at 3 minutes of exercise.46 Takeshita and coworkers48 have observed for the first time that angiographically demonstrable collaterals appeared immediately when coronary arterial spasm was induced by ergonovine in two patients with transient recurrent myocardial ischemia caused by arterial spasm. Similarly, a reduction in coronary luminal diameter by more than 70% was shown to be accompanied by angiographically demonstrable collaterals during coronary occlusion using an angioplasty balloon with 100% specificity and 85% sensitivity.49

Thus, it seems likely that myocardial ischemia serves as a short-term regulatory mechanism for an increase in collateral flow by opening preexistent collateral vessels as well as arterioles in the ischemic region.

**Collateral Growth**

It is now widely accepted that myocardial ischemia50 and/or creation of a pressure gradient across the collateral network somehow triggers collateral growth upon acute coronary occlusion.51 However, the precise nature of the stimulus involved in initiation of collateral development is not fully understood. Schaper51 proposed a working hypothesis about the dominant mechanical influence on the development of collateral vessels. In the early phase of hypoxic collateral dilatation, the tangential wall stress of small interconnecting arterioles resulting from a pressure gradient could initiate vessel remodeling, thereby physical separation of endothelial cells may release the cells from their stringent contact inhibition and activate endothelial cells to proliferate.52 With a canine experimental model developed by Franklin's group,50 the effects of different types of repeated coronary occlusion on collateral development were assessed.53,54 These studies demonstrated that myocardial ischemia of 2 minutes provided sufficient stimuli for angiogenesis, but myocardial ischemia of less than 1 minute failed to stimulate development of collaterals. Although these studies failed to distinguish between the relative contributions of ischemia-related humoral substances and increased tangential wall stress of collateral vessels secondary to ischemia in stimulating neovascularization, these findings provided further support for the importance of these two factors in producing functionally significant collateral vessels.

Chilian et al55 produced multiple microvascular occlusions in anesthetized dogs by partially embolizing the circumflex coronary artery perfusion territory with 25-μm-diameter microspheres so that resting blood flow velocity was not altered but coronary vasodilator reserve was greatly attenuated. This procedure allowed the production of focal areas of ischemia without causing alterations in pressure gradients between large coronary arteries. Partial embolization of the coronary microcirculation was shown to result in the growth and development of coronary collaterals. Therefore, it was emphasized that ischemia, per se, can be a sufficient stimulus to induce coronary collateral development.

These observations support the hypothesis that collateral growth can be induced by a chemical signal from the ischemic myocardium rather than a mechanical force acting on the vessel wall. Development of collateral circulation by myocardial ischemia can best be explained by upregulation or increased externalization of a growth receptor in endothelium and in smooth muscle in response to myocardial ischemia. A biochemical signal produced by ischemic myocardium then triggers the events leading to DNA synthesis and to mitosis in collateral vessels.56,57
Unger and coworkers\textsuperscript{48} developed a canine model in which the left internal mammary artery was implanted in an intramyocardial tunnel into the territory of the left anterior descending coronary artery, the latter being gradually occluded with an ameroid constrictor to render its perfusion territory collateral-dependent during a period of several weeks. Then they found that angiogenesis was established between the implanted extra cardiac artery and the left anterior descending coronary artery and that these anastomoses were capable of providing significant nutritive flow to myocardium at risk in seven of 12 dogs. In this experiment, an independent artery was in contact with the ischemic zone, and angiogenesis occurred. Therefore, regional ischemia was again considered to have provided a stimulus for collateral proliferation.

Scheel and Williams\textsuperscript{59} rendered dogs anemic to a hematocrit of 11 vol\% for 4 weeks and observed an increase in vascularization of both coronary and collateral circulation. In this model, coronary collateral vascularization was increased because of tissue hypoxia in the absence of a pressure difference across the collateral network. When dogs were exposed to hypoxic hypoxemia at simulated high altitude for 1–7 months, however, collateral flows were not significantly different from those of control animals.\textsuperscript{60} Comparing the above two results, these authors concluded that oxygen availability rather than blood flow velocity is most likely linked to vascular growth.\textsuperscript{60}

In the clinical setting, we have shown that angiographically demonstrable collaterals at the onset of acute myocardial infarction are closely related to repetitive preinfarction angina.\textsuperscript{14} It has been indicated that acute myocardial infarction itself causes a significant development of collateral circulation.\textsuperscript{61–63} All of these clinical observations consistently support the importance of recurrent and severe myocardial ischemia for collateral vascular growth.

**Growth Factors and Angiogenesis**

It has long been noted that a large number of mast cells gather around rapidly growing capillaries in chronic inflammation or in the vascularized areas of tumors.\textsuperscript{64} It remained unclear, however, why mast cells were associated with neovascularization. Subsequently, Kessler et al\textsuperscript{65} showed that there was a 40-fold increase in the density of mast cells surrounding the pellet of tumor extract. In contrast, mast cells alone did not cause angiogenesis. From these observations, mast cells were assumed to potentiate capillary growth but not to induce it. Azizkhan et al\textsuperscript{66} supported this concept by demonstrating that mast cells increased endothelial cell migration as the earliest event in the formation of a capillary sprout.\textsuperscript{67} They also found that increased endothelial migration occurred at a heparin concentration of 10 \( \mu \text{g/ml} \), although other mast cell products (e.g., histamine, trypsin, and so on) could not stimulate endothelial migration. In 1982, Taylor and Folkman\textsuperscript{68} demonstrated that heparin could facilitate angiogenesis induced by tumor extracts from human hepatoma cells implanted on the chorioallantoic membrane of the chick embryo. Thus, these data suggested a new function of heparin as a positive regulator of angiogenesis.

Over the past decade, numerous angiogenic factors have been purified and their amino acid sequences determined with subsequent gene cloning.\textsuperscript{69} An uncharacterized small-molecular-weight factor (less than 1,000 daltons) that stimulates angiogenesis in vivo has been isolated from the heart in patients with recent myocardial infarction.\textsuperscript{70} Rabbit myocardium also contains a factor that potentiates large-vessel endothelial cell proliferation in vitro, which is released in higher amounts by increasing ischemia.\textsuperscript{71} Since the discovery that a tumor-derived endothelial mitogen binds to heparin with high affinity,\textsuperscript{72} heparin-binding growth factors have been identified in virtually all tissues examined. Recent studies have demonstrated clearly that both acidic and basic fibroblast growth factors do exist in the heart.\textsuperscript{73–76}

Although heparin alone does not initiate angiogenesis, it potentiates the mitogenic activity of the acidic fibroblast growth factor.\textsuperscript{77} The mechanisms responsible for angiogenic stimulation of heparin are avidly being sought. Until now, two possible mechanisms have been proposed: 1) heparin increases the binding of the endothelial cell growth factor to endothelial receptors,\textsuperscript{78} and 2) heparin protects the fibroblast growth factor from inactivation.\textsuperscript{79}

On the basis of the laboratory data reported by Taylor and Folkman\textsuperscript{68} that heparin potentiates angiogenesis induced by tumor extracts in the chick embryo, Fujita et al\textsuperscript{80} further investigated the effects of heparin on the collateral development by means of repeated brief occlusions. In eight control dogs, 2-minute coronary occlusions were repeated 129±44 times before acute occlusion was no longer accompanied by a reduction in systolic shortening of the ischemic area or by a significant reactive hyperemia upon release. In another eight dogs pretreated with heparin, however, only 81±33 occlusions were needed to produce the same results.\textsuperscript{80}

Subsequently, Unger et al\textsuperscript{81} also assessed the potential of heparin in their newly developed canine model, in which angiogenic agents could be targeted locally to promote neovascularization of a collateral-dependent area of the heart.\textsuperscript{58} They placed ameroid constrictor on the left anterior descending artery, implanted the left internal mammary artery as a collateral source in its perfusion territory with an infusion catheter, and delivered heparin directly to the site of neovascularization. They observed that selective infusion of heparin into the internal mammary artery promoted the formation of anastomoses between this artery and the myocardial circulation more effectively.\textsuperscript{81}

Thus, these findings indicated that heparin has the potential to accelerate the rate of collateral development in vivo.

**Treatment of Effort Angina With Heparin**

The literature contains numerous examples of patients who had complete occlusions of the major branches of the coronary artery but remained free from dysfunction of the ventricular wall motion or myocardial infarction.\textsuperscript{82} This evidence again supports the important functional role of collateral circulation for incremental preservation of cardiac function. In this regard, we attempted to promote collateral development in pa-
patients with angina pectoris by repeated exercise stress combined with treatment with heparin. In 16 patients with obstruction of at least one major coronary artery and angina on effort, exercise was performed according to the standard Bruce protocol twice a day. Ten patients were given an injection of heparin (5,000 units i.v.) 10–20 minutes before each exercise test, and the remaining six patients exercised without heparin treatment. Treatment with heparin increased the total exercise duration from 6.3±1.9 to 9.1±2.2 minutes (p<0.001) and the maximum rate–pressure product from 18,900±5,100 to 25,500±6,800 mm Hg×beats per minute (p<0.001) (Figure 3). After heparin administration, the rate–pressure product was also increased by 35% (p<0.01) at the onset of angina and by 19% (p<0.05) at the point at which ST segment depression (≥0.1 mV) first appeared. All of these variables remained unchanged for the six patients who did not receive heparin. Furthermore, coronary arteriography revealed a significant increase in the extent of collateral circulation to the region perfused by the completely obstructed coronary artery in patients treated with heparin (Figure 4). These findings suggest that heparin facilitates collateral development stimulated by exercise-induced myocardial ischemia in humans. It has also been found that heparin treatment without exercise does not improve exercise capacity in patients with effort angina. Thus, it may logically be concluded that heparin does not initiate but rather accelerates the collateral development induced by myocardial ischemia.

More recently, we examined the effects of intravenous heparin on potentiation of the collateral develop-

FIGURE 3. Bar graphs show exercise time and double products (maximal [MAX], at the onset of angina [ONSET], and at 0.1 mV ST segment depression) before (open bars) and after 20 rounds of treadmill exercise according to standard Bruce protocol with pretreatment with heparin (5,000 units i.v.) (hatched bars) in 10 patients with chronic effort angina. *p<0.05, **p<0.01, and ***p<0.001 compared with values before heparin–exercise treatment. All of these variables of exercise capacity remained unchanged in an additional six patients who had the same serial exercise periods without heparin pretreatment.

FIGURE 4. Coronary arteriograms of one representative case. Patient is a 63-year-old woman. For the previous 2 years, the patient had had typical anginal pain on effort. With heparin–exercise treatment, total exercise duration increased from 6 to 8 minutes, with maximal double product augmented by 30%. Before treatment, right coronary arteriography showed a 75% narrowing at its proximal portion, and septal arteries were opacified only incompletely (panel A). After treatment, both number and size of septal arteries were markedly increased (panel B).
ment in patients with acute myocardial infarction. Angiographically, the extent of collateral circulation was shown to be more pronounced in the patients with intravenoue heparin during the acute stage of infarction. Left ventricular function was also well preserved in these patients.

Although these clinical investigations have been conducted in small numbers of patients, in nonrandomized and unblinded studies, there is a possibility that ischemic heart disease may be treated with drugs to increase the development of collateral blood vessels. The development of such a therapeutic remedy would attenuate the deleterious sequelae caused by coronary atherosclerosis.

Summary
The functional significance of coronary collateral vessels in humans has been debated for many years. Correlations have now been made between the anatomic appearance of coronary collateral vessels visualized at the time of intracoronary thrombolytic therapy during the acute phase of myocardial infarction and the creatine kinase time–activity curve, infarct size, and aneurysm formation. These studies demonstrate a protective role of collaterals in hearts with coronary obstructive disease, showing smaller infarcts, less aneurysm formation, and improved ventricular function compared with patients in whom collaterals were not visualized.

There is ample evidence that collaterals respond to myocardial ischemia by opening preexistent channels. When the cardiac myocyte is rendered ischemic, collaterals develop actively by growth with DNA replication and mitosis of endothelial and smooth muscle cells.

Heparin-binding growth factors are present in the heart, but their biological activity is quiescent under normal physiological conditions. Once ischemia develops, these factors are activated and become available for receptor occupation, which may initiate angiogenesis after exposure to exogenous heparin.

This characteristic of heparin to potentiate the mitogenic activity of acidic fibroblast growth factor has recently been used in the clinical setting as a possible therapeutic modality in patients with coronary artery disease. Patients performing 20 rounds of exercise serially after receiving intravenous injection of heparin showed significantly greater increases in exercise capacity and improvement of clinical symptoms compared with the control group who performed the same exercise without heparin. Further study of neovascularization may lead to a new therapeutic strategy for ischemic heart disease.

Thus, recent basic and clinical investigations have elucidated the importance of the coronary collateral circulation for protection of compromised myocardium during severe coronary stenosis. A complete understanding of the precise mechanism of angiogenesis could lead to the development of new drugs capable of enhancing angiogenesis of collateral vessels more effectively in patients with coronary artery disease.

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