Coronary Collaterals Revisited
Accessory Pathway to Myocardial Preservation During Infarction

Eric J. Topol, MD, and Stephen G. Ellis, MD

In the setting of reperfusion therapy for acute myocardial infarction, several studies have indicated the importance of coronary collaterals for subsequent improvement of cardiac function or reduction of infarct size. Habib and colleagues have reported in this issue of Circulation a detailed post hoc analysis of coronary collaterals from the Thrombolysis in Myocardial Infarction (TIMI) Phase I trial. In this study of 125 patients from TIMI-I who had an occluded infarct vessel at baseline angiography and 90 minutes after intravenous thrombolytic therapy, the 51 patients (41%) with demonstrable collaterals had (compared with patients without collaterals) a 35% reduction in infarct size by creatine kinase methodology and a relative 12% improvement in ejection fraction (+2.7 versus −2.4 units) by paired contrast ventriculography.

These findings confirm earlier observations with intracoronary thrombolytic therapy. Rogers and associates analyzed patients with failed reperfusion but collaterals to the infarct territory (n=18), which they termed “limited flow,” together with a smaller group of patients who achieved reperfusion but were left with a subtotal coronary occlusion at baseline (n=9). After streptokinase treatment, patients with “limited flow” compared with total occlusion had a 50% reduction of creatine kinase peak and a relative 11% improvement of ejection fraction.

More recently, Rentrop et al suggested that the presence of coronary collaterals “extends the time window” for the beneficial effect of reperfusion therapy. In the second Mount Sinai–New York University Reperfusion Trial with paired measurement of cardiac function at baseline and at a time 10–14 days later, patients with collaterals receiving combination streptokinase and nitroglycerin (n=18) had a substantial improvement in ejection fraction of 9.8%, while those without collaterals (n=25) had a 0.8% decline in ejection fraction. A previous report from the TIMI-I investigators has also supported the importance of collaterals for incremental preservation of cardiac function.

Collectively, these studies suggest that patients with angiographically visible collaterals at the time of thrombolytic therapy initiation have an advantage. Approximately 40% of patients will have grade 2 or 3 collaterals at the time of early angiography and this group can be expected to have a better pre-discharge ejection fraction and a lower peak creatine kinase value. Hirai and coworkers have pointed out that collaterals are a key determinant of the creatine kinase time activity curve; patients with persistence of collaterals after intracoronary urokinase not only had lower values of creatine kinase activity but their peaks were significantly delayed compared with those of patients with successful recanalization (yet earlier than those of patients with failed thrombolytic therapy, with collaterals). Thus, collaterals clearly do provide some perfusion to the infarct territory and contribute to the washout pattern of creatine kinase. With respect to the interaction of successful thrombolysis and collaterals, it appears there is most benefit for patients with successful thrombolysis and collaterals at baseline but that the benefit extends even to patients with unsuccessful thrombolysis but collaterals present from the time of coronary occlusion.

Mechanism of Benefit
A major unresolved question with coronary collaterals in the setting of myocardial reperfusion is the mechanism of benefit. Is this simply a matter of providing an alternative conduit with reduced, partial flow to the infarct territory? Or is the benefit in collaterals related to enhanced delivery of thrombolytic therapy with increased likelihood of early or even delayed recanalization?

One would expect to particularly impact subepicardial flow in the presence of collaterals. With the wavefront of necrosis extending last to this region, it is possible that prevention of an epicardial rim of tissue may occur. Indeed, Hirai et al have recently demonstrated a link between the presence of collaterals and protection from left ventricular aneurysm.
formation. In 10 patients with unsuccessful reperfusion with collaterals present, only one subsequently developed an aneurysm while seven of 12 patients (58%) without reperfusion or collaterals had aneurysm formation. Further protection from infarct expansion in this study was conferred by delayed, spontaneous recanalization or delayed appearance of collaterals evident at angiography reassessment 1 month later. It remains possible that retrograde filling by collaterals may have benefit equivalent to that of delayed restoration of antegrade flow. In experimental studies by Hochman and Choo and Hale and Kloner, late antegrade flow was associated with improved granulation and healing of the infarct territory and less infarct expansion.

An intriguing explanation for the salutary effect of collaterals is enhanced delivery of fibrinolytics to the occlusive thrombus. While this has not yet been specifically addressed by experimental or clinical studies, the presence of collaterals might facilitate thrombolysis. In a canine pulmonary embolism model, Prewitt et al have shown how critically dependent flow is on the success and extent of thrombolysis. Use of coronary sinus retroperfusion, which can be thought of as partially mimicking retrograde filling via collaterals, has demonstrated successful thrombolysis by retrograde venous delivery after systemic or antegrade coronary artery therapy was unsuccessful. Because at least 25% of patients fail systemic thrombolytic therapy 90 minutes after it is begun, and we know that approximately half of these patients eventually exhibit successful recanalization by 24 hours, collateral delivery of plasminogen activators to the persistently occluded site may be quite important. Delayed coronary recanalization is more frequent with plasminogen activators lacking fibrin specificity, such as streptokinase. The attendant decrease in viscosity and improvement in microcirculatory flow may further enhance the collateral effect and amplification of clot lysis.

Implication for Therapy

Our understanding of the apparent benefit of collaterals, irrespective of the precise mechanism, begs the question of what can be therapeutically implemented to take advantage of this finding. For example, should all patients receive high doses of intravenous nitroglycerin in combination with thrombolytic therapy? This is a difficult question to answer, given what is already a multidrug regimen that now typically includes aspirin, heparin, and β-blockers. Certainly a meta-analysis performed by Yusuf and colleagues using studies that antedated the era of myocardial reperfusion provided strong support for the use of nitrates. On the other hand, there has been only one randomized study of nitroglycerin with thrombolytic therapy, and although suggestive of a streptokinase-nitroglycerin favorable interaction, this was using intracoronary administration. Recently, intravenous nitroglycerin has been implicated in a negative pharmacological interaction with both heparin (diminishing its anticoagulant effect) and tissue plasminogen activator (reducing its fibrinolytic action). Thus, while intriguing, the use of adjunctive therapies to promote collateral flow is far from settled and deserves careful study in the future.

Reperfusion therapy late after symptom onset may prove beneficial, as even patients who presented 6–24 hours after chest pain began exhibited improved survival with streptokinase compared with placebo in the International Studies of Infarct Survival (ISIS)-2 trial. The benefit of thrombolytic therapy may be relatively confined to patients with collaterals, who could stand to derive the most benefit of delayed coronary artery recanalization. It will be important to consider the role of collaterals in interpreting the data from ongoing clinical trials of reperfusion for late entry patients.

A third area that may be affected by collaterals is rescue coronary angioplasty for patients with unsuccessful thrombolysis. In considering this intervention for a patient with grade 3 collateral flow, there needs to be close scrutiny for the trade-off of mechanical embolization of fibrin or plaque contents, which in some cases could occlude the collateral supply. On the other hand, when the infarct vessel is patent but collaterals are still present and the patient has signs of ongoing ischemia, this may be interpreted as inadequate perfusion mandating revascularization with angioplasty or bypass surgery.

Key Limitations

It is important to point out that angiographically visible collaterals represent only a fraction of collateral circuitry. Using angiography, we can only visualize channels more than 100 µm in diameter, giving no insight regarding the microcirculation. Furthermore, this epicardial arcade of vessels may not reflect the presence of intramyocardial collateral circulation. The development of collateral circuits does not seem to follow expectations that a tight, preexisting stenosis need be present; Edwards and Little reported a patient with immediate collateral recruitment despite absence of a stenosis. Indeed, “new” collaterals can frequently be demonstrated during coronary angioplasty.

The presence of angiographic collaterals is thus very dynamic; the study by Habib et al1 represents a “snapshot” assessment 4–5 hours after symptomatic coronary artery occlusion began. Determination of grade 2 collateral flow requires systematic prolonged cineangiography after contrast injections. Now that we can no longer withhold intravenous thrombolytic therapy for eligible patients with evolving myocardial infarction for a control angiogram, it will be extremely difficult to acquire meaningful baseline data regarding the presence of collaterals. Subgroup analysis of patients with and without collaterals is also plagued by our inability to distinguish true cause or effect and by the possibility that the collaterals per se are an epiphenomenon or marker for patients with superior adaptation to defective perfusion.
New, noninvasive enzymatic methods to detect reperfusion rely on early creatine kinase or other protein marker washout, which can occur with reestablished antegrade flow or with collateral blood flow. In an early experience of evaluating creatine kinase isoforms,22 false-positive reperfusion determinations were usually attributed to the presence of collaterals. This could be viewed as inaccurate or misleading. However, with the available data that underscore the beneficial impact of accessory, collateral flow, it may suggest that the absence of either antegrade or collateral perfusion could serve as the key triage point for patients to undergo fallback mechanical reperfusion approaches such as rescue balloon angioplasty. As we continue to refine our pharmacological and mechanical therapies for myocardial reperfusion, it will be vital to be cognizant of the potential impact of coronary collaterals.

References
Coronary collaterals revisited. Accessory pathway to myocardial preservation during infarction.

E J Topol and S G Ellis

Circulation. 1991;83:1084-1086
doi: 10.1161/01.CIR.83.3.1084

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1991 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/83/3/1084.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/