Recognition of the Importance of Embolization in Atherosclerotic Vascular Disease

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It is uncommon in medicine for emerging data to completely transform a field, particularly in such a common disease state as atherosclerotic vascular disease. New evidence from multiple fronts has underscored the frequency and prognostic importance of atherosclerotic embolization in the microvasculature. Until recently, we have had limited access to diagnose microvascular obstruction in living patients. With the availability of imaging technology that includes magnetic resonance, myocardial contrast echocardiography, and transcranial Doppler (TCD), microvascular obstruction has been documented in a far greater proportion of patients than ever conceived. The linkage between microvascular obstruction and unfavorable long-term clinical prognosis has been established in many series. Furthermore, therapeutics shown to reduce microvascular obstruction have improved clinical outcomes. The purpose of this article is to present the case for a disturbingly and unexpectedly high rate of arterial embolization in certain atherosclerotic conditions and to review the promise of newer therapeutics or devices to reduce the risk or ameliorate the sequelae of embolization.

A Change in the Mind-Set

Acute myocardial infarction (MI) has been accepted to be related primarily to a fissured, eroded, or ruptured plaque. This event leads to exposure of subendothelial matrix, with attendant platelet aggregation, thrombus, and occlusion of a major epicardial vessel. In a continuum, unstable angina and non–ST-segment-elevation MI also are indexed to a breech of major epicardial vessels. In Figure 1, a histological view of an obstructed vessel from a patient with sudden cardiac death demonstrates stain for platelet glycoprotein (GP) IIb/IIIa, confirming platelet-thrombus as the occlusive material. Also, atherosclerotic particulate matter from an elective native coronary artery percutaneous revascularization shows in clinical investigation that we have just conducted in >50 patients undergoing elective percutaneous revascularization, all patients had particulate matter retrieved via an embolic filter device (vide infra).

Two recent studies have been especially noteworthy in focusing on endothelial cells. In a recent study of patients with acute coronary syndromes, circulating endothelial cells
were identified at relatively high frequency (compared with control subjects or patients with effort angina) in the peripheral blood.\textsuperscript{14} Using an experimental canine model, Eguchi et al\textsuperscript{15} studied the effect of microvascular obstruction on endothelial function and demonstrated loss of integrity and adherence of platelets and leukocytes. The updated pathophysiology of embolization can be summarized in Figure 2.

Atherosclerotic vessels can be transformed from a stable, quiescent phase to “unstable” when there is inflammation of the arterial wall or intravascular iatrogenic manipulation that is part and parcel of transcoronary revascularization. In both circumstances, there is disruption of the fibrous cap of the plaque with exposure of subendothelial matrix elements. Accordingly, plaque and vessel wall constituents, including lipid, matrix, and endothelial cells, and platelet-thrombus, if present, can embolize. As fully described by Willerson et al,\textsuperscript{13} this sets up the potential for microvascular obstruction, with loss of endothelial integrity, release of vasoactive amines from activated platelets, increased vascular tone, and potentiation of platelet-thrombus.

New Window to Microvascular Obstruction

Our awakening to the frequency of microvascular obstruction was made possible through an array of newer diagnostic imaging modalities. One of the early studies, which took the cardiovascular community by surprise, was performed by Ito and colleagues.\textsuperscript{16} Using myocardial contrast echocardiography, they showed that \( \geq 25\% \) of patients with what appeared to be brisk epicardial flow (using conventional contrast dye angiographic assessment) did not have tissue level reperfusion (Figure 3).

\textbf{Figure 3.} Top, Proportion of patients who have perfusion defect by myocardial contrast echocardiography (MCE) as function of TIMI grade. Bottom, Example of patient with TIMI grade 3 flow of infarct vessel with myocardial contrast echocardiographic defect. (Adapted from data in Reference 16.)
reperfusion injury. Recently, Wu and colleagues\textsuperscript{17} used MRI of the infarct myocardium to show that microvascular obstruction carried a grave prognosis (Figure 4). This pattern of obstruction could be delineated very early after the onset of MI, making inflammation, edema, and reperfusion injury a less likely explanation than atherosclerotic and platelet-thrombotic obstruction.

Using TCD during carotid stenting procedures, Jordan and colleagues\textsuperscript{18} have now demonstrated that virtually every patient undergoing the procedure has Doppler evidence of microembolization (Figure 5). With the use of nuclear scintigraphy with sestamibi in patients undergoing coronary rotablation, intraprocedural perfusion defects have been duly noted, despite a lack of enzymatic evidence of myocardial necrosis (Figure 6).\textsuperscript{19}

Besides direct imaging with echocardiography, magnetic resonance, and scintigraphy, there have been extensive new insights derived from markers of myocardial necrosis. Several years ago, the Coronary Angioplasty Versus Excisional Atherectomy (CAVEAT) investigators demonstrated for the first time in a large prospective trial that the incidence of periprocedural MI was much higher than generally accepted.\textsuperscript{20} By using the physician-investigator’s recording, they found the infarct rate to be 3% for PTCA and 6% for atherectomy. By use of a core laboratory that adjudicated the clinical events with all the creatine kinase (CK) and myocardial band isoenzyme data that were systematically collected, the incidence of periprocedural MI (with a 3-fold increase over baseline value of creatine phosphokinase, CK-MB

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure4.png}
\caption{Top, Event-free survival (clinical course without cardiovascular death, reinfarction, congestive heart failure [CHF], or stroke) for patients with and without MRI microvascular obstruction. Bottom, MRI from patient with anteroseptal infarct and extensive subendocardial microvascular obstruction (between arrows). Figure reprinted with permission from \textit{Circulation}. 1998;97:765–772. ©1998, American Heart Association.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{TCD monitoring of middle cerebral artery during elective carotid artery stent procedure demonstrating high-intensity transients representing emboli released after balloon deflation.}
\end{figure}

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure6.png}
\caption{Top, Incidence of patients undergoing rotablation with perfusion defects according to treatment group. Bottom, SPECT images obtained before and during rotablation in patient with lesion of left anterior descending artery and previous inferior MI. Sagittal long-axis views are displayed, indicating transient apical perfusion defect. Bottom figure reprinted with permission from \textit{J Am Coll Cardiol}. 1999;33:998–1004. ©1999, American College of Cardiology.}
\end{figure}
threshold) was 8% for balloon angioplasty and 19% for directional atherectomy. In the subsequent CAVEAT-II trial of saphenous vein graft intervention, the MI rates were considerably higher at 15% and 24%, respectively. This finding set off a debate as to whether there was any clinical significance of the "enzyme leaks," "infarctlets," "CK bumps," "CK efflux events," or "microinfarcts." In the long-term follow-up of CAVEAT, there was a significant excess of mortality for atherectomy, and most patients who died in this group had experienced a periprocedural non–ST-segment-elevation MI. Several large series of patients were assessed to determine whether there was a relationship with periprocedural MI and outcome; indeed, a remarkable correlation has been established. The higher the CK elevation, the more risk of death during follow-up was demonstrated by Abdelmeguid et al., Kong et al.,26 and many others.27–29

As shown in Figure 7, there is a striking relationship of mortality rate as a function of increase in periprocedural CK-MB elevation in the 3 randomized trials of percutaneous coronary revascularization with abciximab or placebo. The risk of periprocedural MI also related to the type of coronary revascularization, with the highest likelihood induced by directional atherectomy, followed by rotational atherectomy and then stenting and least incidence with balloon angioplasty. Thus, the diffuseness of atherosclerotic disease and invasiveness of the revascularization technique with respect to vessel wall injury emerged as 2 dominant risk factors.

Interestingly, little else could be invoked to explain the very high rate of periprocedural MI besides embolization. The time of ischemia during balloon inflation, device manipulation, or stent deployment is generally much too short to result in myocardial necrosis. Side branch closure is very infrequent, in <3% of recent trials. Transient or abrupt closure occurs only in <1% of patients, and the actual time of ischemia in such patients is usually limited to a matter of minutes. Without alternative explanations, the differential diagnosis leaves embolization with microvascular obstruction as the leading suspect.

The incidence of myocardial necrosis is even higher if one turns to a much more sensitive marker, troponin (I or T). With this test, the incidence of some myocardial necrosis in patients undergoing routine coronary revascularization is between 30% and 40%. This suggests that embolization is extraordinarily common and that a large minority of patients actually suffer some extent of measurable myocyte damage. Perhaps most patients still experience some embolization but do not go on to myonecrosis either because the burden of particulate matter is much less or because there are adaptive responses to accommodate the process.

Recent data from troponin in patients with unstable angina have been particularly illuminating. In the Chimeric 7E3 Antiplatelet Therapy in Unstable Angina Refractory to Standard Treatment (CAPTURE) trial, abciximab or placebo was administered, and the primary end point of death or nonfatal MI was assessed in the short term, along with 6-month follow-up. As shown in Figure 8, Hamm et al. differentiated the response to therapy as a function of troponin T at baseline. Patients who had an abnormal troponin T level were remarkably sensitive to therapy with abciximab. It is most likely that the patients who presented with elevated troponin T level were remarkably sensitive to therapy with abciximab. It is most likely that the patients who presented with elevated troponin levels already had developed microvascular obstruction as a result of embolization. By virtue of platelet disaggregation with GP IIIb/IIIa blockade, the relief of microvascular ob-

![Graph 1](http://circ.ahajournals.org/)

![Graph 2](http://circ.ahajournals.org/)

**Figure 7.** Top, Mortality for patients with 1- to 10-fold increases in periprocedural CK elevation vs patients without CK elevation in EPIC trial. Middle, Mortality rates for patients with 1- to 10-fold increases (within 24 hours) in CK-MB elevation in EPICLOG trial. Bottom, Mortality rates for patients by enzyme level in EPISTENT trial. Top figure reprinted with permission from *JAMA*. 1997;278:479–484. ©1997, American Medical Association. Middle figure reprinted with permission from *Circulation*. 1999;99:1951–1958. ©1999, American Heart Association.
struction would be anticipated. All along, it was thought that the predominant explanation for the benefit of GP IIb/IIIa antagonism in the setting of unstable angina was to reduce thrombus in the culprit epicardial artery. But this therapeutic tenet would not provide a foundation for explaining the marked sensitivity that patients with myocardial necrosis have for GP IIb/IIIa antagonism. In addition to reducing the propensity for clot formation at the site of arterial injury, there must be a substantial component of benefit derived from improving microcirculatory perfusion.

Mechanical Approaches

Besides pharmacological agents capable of dealing with the response to embolization, a more direct method of addressing the problem would be to prevent the particulate matter from traversing distally. Recently, a few devices have been designed to trap embolic material. Two devices, the PercuSurge and Angioguard systems, are shown in Figure 9. These devices fall into 2 general types: distal balloons that occlude the artery during intervention with aspiration of debris with a small catheter (PercuSurge), and filters that trap debris during intervention and are then collapsed and withdrawn from the artery with the trapped debris (Angioguard). The PercuSurge and Angioguard devices have had initial clinical testing and have provided “smoking gun” evidence that embolic material is present in far more patients than was previously conceived. PercuSurge has been applied to patients undergoing saphenous vein graft and carotid stenting, and in almost all cases, embolic material that would have otherwise reached the distal vasculature was retrieved. The Angioguard basket approach has been tested in patients undergoing percutaneous coronary, renal, and saphenous vein grafts and carotid intervention, with retrieval of atherosclerotic material in every patient (Figure 1).

Some limitations of the devices are important to highlight. The balloon occlusion-type devices cause distal ischemia that may not be tolerated by some patients, and an aspiration catheter may not remove all particles trapped in the artery. In addition, angiography cannot be performed while the distal balloon is inflated, making assessment of the artery and stent placement more difficult. The filter-type devices have a finite lower limit in the size of particles that can be captured; the practical lower limit for pore size appears to be 50 μm. Smaller microparticulate matter can still get through the filter, although particles that small may have no clinical significance. It is still early in the development of these novel catheter- and guide-wire–based systems; making them as atraumatic as possible, with the lowest profile and highest torqueability, will require further iterative engineering. Without question, there will be several emboli protection devices that evolve and ultimately are incorporated into the daily practice of percutaneous coronary and peripheral revascularization.

Pharmacological Therapeutics

Supporting the importance of microvascular obstruction, there are several pharmaceutical agents that have provided strong evidence of clinical benefit. While it is likely that some benefit is mediated through effects at the epicardial or large artery (eg,
carotid) level, the microcirculation must play a pivotal role. Several examples provide evidence for this assertion.

In a randomized trial by Neumann et al., 40 200 patients with acute MI who were undergoing primary stenting and reperfusion were randomly assigned to abciximab or heparin. As shown in Figure 10, coronary blood flow was substantially improved in the infarct zone for abciximab-assigned patients as assessed by Doppler with adenosine provocation. Along with this finding, there was a significant improvement in regional and global ejection fraction compared with control (conventional) therapy.40 This represents the first myocardial reperfusion study to show that further augmentation of microvascular perfusion is associated with improved myocardial performance. This mechanistic study of abciximab is flanked by several large-scale clinical trials of the platelet GP IIb/IIIa inhibitors,41–49 all of which show a reduction in the short duration of platelet IIb/IIIa inhibitor therapy during percutaneous coronary intervention could achieve a reduction in long-term mortality.30 An attractive explanation, in light of the new data showing the likely ubiquitous nature of emboli induced by percutaneous coronary revascularization, is protection of the microvasculature. A watershed zone infarct, albeit small in terms of myocardial mass damaged, is of critical importance in lowering the threshold for ventricular arrhythmias. The data that support the propensity of arrhythmias in patients who have periprocedural MI show that most of the deaths are sudden, as demonstrated by Abdelmeguid et al.32 and in the recent EPISTENT trial. Therefore, at least 1 explanation for a durable benefit of short-term IIb/IIIa blockade invokes the avoidance of microvascular obstruction, the attendant myocardial necrosis, and predicted risk for subsequent malignant arrhythmias. It needs to be emphasized that abciximab or other IIb/IIIa inhibitors would not be expected to reduce embolization of atherosclerotic lipid and matrix constituents. On the other hand, the putative mechanism of benefit is most likely tied to avoidance of platelet aggregation in the microcirculatory zone, which has been the recipient of embolic material.

Other therapeutic agents have shown improvement in microcirculatory perfusion and may have a role in favorably modulating the response to embolization. In a randomized trial of intracoronary verapamil in 40 patients who had catheter-based reperfusion, there was improved tissue level perfusion, reflected by myocardial contrast echocardiography, compared with placebo.50 Besides calcium channel blockade, the agent nicorandil, an ATP-sensitive K+ channel opener with vasodilating action, was also recently shown to improve microcirculatory perfusion in the infarct territory.51 In a randomized trial of 81 patients with primary PTCA for anterior MI, the incidence of myocardial contrast echo perfusion defects was reduced from 34.1% to 15% (P < 0.001), and mortality was reduced from 10% to 0% (P = 0.043).51 The benefit of an agent such as nicorandil may be at the level of improving endothelial function in the affected microvascular territory. The platelet-thrombus response to embolization in the setting of unstable angina may also be diminished by improved anticoagulation. With the low-molecular-weight heparin dalteparin, there was a substantial reduction in death or nonfatal MI among patients in the Fragmin During Instability in Coronary Artery Disease (FRISC) trial who had abnormal baseline troponin levels.52 This finding suggests the concept that therapies directed to either platelets or the coagulation system might be effective in clinical settings in which embolization is prevalent.

**Profile of “The Embolizer”**

The changed perspective of the prominence of embolization leads to a rethinking of our understanding of and approach to several diseases and procedures that share atheromatous substrate. We can now begin to recognize a certain profile of patients as “the embolizer,” individuals who are most apt to shower emboli at the time of a revascularization procedure or at clinical presentation. With respect to pathological substrate, the diffuseness of disease, friability of the atheroma-
tous lesion, and presence of platelet-thrombus would seem to be the most likely predisposing features once an artery was manipulated. Disruption of the fibrous cap of atherosclerotic plaque, the histopathological basis of acute coronary syndromes, surely identifies a patient group quite prone to embolize. The friability may well be linked to ongoing inflammation, because many recent studies have underscored the prominent effect that elevation in C-reactive protein, necrosis factor-\(\text{TNF}\), interleukins, or vascular adhesion molecules and other inflammatory markers have on long-term prognosis.\(^{53-57}\) Of demographic features, diabetes mellitus stands out as 1 with particular risk, such as increased mortality after coronary intervention.\(^{58}\) This could be attributed to the diffuseness of atherosclerotic involvement, extent of preexisting microvascular disease that reduces the adaptive capacity to embolization, or heightened inflammation related to insulin, S-glycolation products, or other metabolic factors. There may well be genotypic features that will be useful for identifying patients who have a propensity to embolize or cannot accommodate particulate matter.

Figure 10. A Left, Effect of stroke with and without GP IIb/IIIa inhibition (GPI) on platelet and fibrin accumulation in brain. \(^{111}\)In-labeled platelets were administered to control mice; 24 hours later, brains were harvested, divided into right and left hemispheres, and counted. Relative platelet accumulation is expressed as ratio of right/left hemispheric counts per minute. Right, Immunostaining for fibrin in contralateral (top right) and ipsilateral (top left) cerebral hemispheres 24 hours after stroke. Microvessels are indicated with arrows. Intravascular fibrin formation can be seen as red staining in postischemic microvasculature. When GPI was administered before stroke, there was no apparent reduction in microvascular fibrin accumulation at 24 hours (bottom). B. Plot of differences between 14-day follow-up and initial postinterventional study in basal flow velocity and in papaverine-induced peak flow velocity at treated lesion. Columns represent mean difference. Error bars indicate 95% CI; \(P=0.15\) for basal and \(P=0.024\) for peak. C, Improvement in wall motion index (SD/chord) rejection fraction with use of abciximab with primary stenting. Figure 10A reprinted with permission from J Clin Invest. 1998;102:1301–1310. ©1998, American Society for Clinical Investigation. Figures 10B and 10C reprinted with permission from Circulation. 1998;98:2695–2701. ©1998, American Heart Association.
Clinical Conditions

Percutaneous Coronary Intervention

To reduce the incidence of periprocedural MI, inhibition of platelet function more than that achieved with aspirin monotherapy appears to be clearly justified. Preprocedural therapy with combination aspirin and clopidogrel or ticlopidine should be considered in light of new observational data that show a significant reduction in MI events, presumably stemmed from modulating the response to embolization.60 A dedicated, prospective trial is ongoing to address the specific question of dual preprocedural antiplatelet therapy. Although cost issues are significant, intravenous platelet GP IIb/IIIa agents would ideally be used in all patients. This can be justified on the basis that currently available data show a very substantial reduction in death or nonfatal MI, particularly with abciximab. Lower-cost strategies need to be developed to simulate or surpass the efficacy of this class of agents. Of note, platelet-directed strategies are not squarely addressing the underlying insult. With the refinement and wide-scale availability of emboli protection devices in the future, the need for GP IIb/IIIa inhibition may, at some point, be substantially reduced. One subgroup of patients demonstrated that even state-of-the-art therapy is inadequate to protect against the problem of embolization. Patients with degenerated saphenous vein grafts who undergo percutaneous intervention are at high risk of periprocedural MI, and this risk does not appear to be significantly reduced with GP IIb/IIIa inhibition.60 Whereas saphenous graft lesions were long thought to carry an excessive risk of atherosclerotic gruel dislodgment, the persistent frequency of MI risk and resistance to current therapies point to the need for a better mechanical approach. This finding also suggests that when an embolization mass is quite large, it can override the benefit of platelet-directed therapy.

Another area of concern while more data are garnered is patients who have a bona fide periprocedural MI and have a risk of death proportional to the size of MI during extended follow-up. In these patients, there has been unequivocal myocardial necrosis, but no current approach has been advocated to reduce the risk. Consideration of long-term β-blockade therapy seems appropriate, with the known risk of sudden death, in abeyance of clinical trials that are necessary to resolve this critical question of secondary prevention.

Carotid Intervention

Cerebrovascular intervention is still considered an investigation technique that is being compared with carotid endarterectomy with respect to safety and efficacy; however, there are no completed randomized trials. Both strategies carry an important risk of periprocedural stroke, undoubtedly related to embolization. With TCD, virtually every patient undergoing either form of revascularization has acoustic and Doppler signal evidence of embolization.18 The same principles discussed for coronary intervention apply, with the need for improved preprocedural platelet inhibition, intraprocedural platelet aggregation blockade, and, it is hoped, imminent availability of emboli protection devices to make both forms of revascularization safer. Unlike the heart, there is no readily available enzymatic test of brain necrosis, so the ability to diagnose watershed damage events is impaired. Laboratory methods to track brain damage with these procedures are quite important to develop, because the parallels to the heart for prognosis and refinement of therapies are obvious.

CABG Surgery

It has long been known that a risk of CABG is stroke in 1.5% to 5.2% of patients in prospective studies and is especially pronounced in the elderly. Besides overt stroke, there is a higher risk of cognitive defects such as memory impairment, visuospatial deficits, and depression. These neurological sequelae are all believed to result from emboli.61–64 In the past few years, there has been an emphasis on the presence of atherosclerosis in the aorta as a key risk factor for stroke during open heart surgery.55,66 With TCD, cerebrovascular embolization has been found to occur in essentially all patients, and there is positive correlation between brain injury and embolic burden.61,62 In a meticulous study with TEE and TCD, Barbut and colleagues64 found that particle diameter varied from 0.3 to 2.9 mm (mean, 0.8 mm) and volume varied from 0.01 to 12.5 mm³ (mean, 0.8 mm³). Total aortic embolic load was 0.6 to 11.2 cm³ (mean, 3.7 cm³), and the cerebral embolic load was 60 to 510 mm³ (mean, 276 mm³), with 3.9% to 18.1% of aortic emboli entering the cerebral circulation. The field of CABG is behind other areas of emboli protection, but this direction needs to be pursued. The S100 protein may, like CK-MB or troponin, prove helpful in tracking brain cell necrosis and indirectly reflecting microvasculature obstruction.67 An early study suggests that a filter on the bypass cannula may reduce the number of emboli and release of S100 protein from the brain.63 There should be strong consideration for clinical investigation of the use of emboli protection devices to be placed in the aorta and for improved perioperative antiplatelet therapy. Besides atherosclerotic debris, small capillary/arteriolar dilatations are thought to be lipid-containing emboli that contain aluminum and silicon. Small capillary/arteriolar dilatations are derived from the cardiopulmonary bypass circuit and its tubing.67

Unstable Angina and Non–ST-Segment Elevation

The bedside availability of sensitive markers of myocardial necrosis such as troponin T or I sets up a new-found ability for the clinician to track the likelihood of coronary embolization. Patients with unstable angina with a positive troponin have likely suffered microvascular obstruction and clearly derive pronounced benefit from the use of platelet GP IIb/IIIa inhibitors. We are only in the early phase of revamping our therapies for such patients; a patient who has developed an embolic event may also have significant inflammation of the diseased coronary artery. In fact, a recent study showed the prognostic interdependence and additivity of troponin and C-reactive protein.56 Thus, such patients may require improved anti-inflammatory strategies that have yet to be tested in clinical trials. Furthermore, long-term augmentation of antiplatelet therapy such as the addition of an ADP receptor antagonist or oral GP IIb/III inhibitor may be necessary.
Stroke

Only a small proportion of patients with evolving stroke are eligible for intravenous fibrinolytic therapy with tissue plasminogen activator.68 However, the prothrombotic deficiencies of tissue plasminogen activator, along with an inability of any plasminogen activator to address the platelet-rich white thrombus, undermine the therapeutic efficacy. Indeed, the data have been mixed or marginal for the fibrinolytic approach.69 Perhaps a key further explanation is the lack of attention to relieving microvascular obstruction, which would potentially be exacerbated by fibrinolytic therapy alone. In a recent experimental stroke model, Choudhri et al70 showed marked sparing of brain infarction and relief of microvascular obstruction using a platelet GP IIb/IIIa inhibitor. Initial experience with GP IIb/IIIa blockade in acute stroke management had indeed been quite favorable.71 It is likely that a combined low-dose fibrinolytic, full–GP IIb/IIIa blockade strategy will be useful in achieving brain salvage in acute cerebrovascular thrombosis.

Acute MI

A major problem in the treatment of acute MI is the potentiation of bulk fibrin emboli, which is promoted by either fibrinolytic therapy or catheter-based reperfusion therapy. Interestingly, a recent trial of stenting compared with balloon angioplasty showed no improvement in flow achieved and actually a decrease for stenting.72 With the increased use of stenting as the mainstay of catheter-based reperfusion, the problem of emboli of atherosclerotic gruel in addition to platelet-thrombus is exacerbated. Use of improved antiplatelet therapy, such as that shown with GP IIb/IIIa inhibition,40,44 and ultimately the application of emboli entrapment devices in this setting can be anticipated. Another alternative or adjunct to emboli entrapment may be the use of ultrasound fibrinolysis catheters, which can fully dissolve the coronary thrombus and reduce the potential of bulk emboli.73 Initial results in clinical trials for improving myocardial perfusion and regional wall motion of the infarct zone beyond conventional therapy are encouraging.73

With pharmacological strategies, there are intrinsic obstacles that need to be surmounted. The paradoxical prothrombotic effects of plasminogen activators set up the potential for more accumulation of thrombus,74 particularly in the low-flow watershed zone of the infarct. The current approaches do not include any acute platelet-directed strategy except for the modest effects of chewable or orally administered aspirin. For this reason, we and others have embarked on a new reperfusion strategy that is primarily platelet directed75,76 using fibrinolytic therapy in lower doses as an adjunct. The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded arteries (GUSTO-4) 16 600-patient acute MI trial is currently testing the hypothesis that GP IIb/IIIa inhibition with abciximab and low-dose reteplase will be superior for survival compared with conventional reteplase dosing. Pilot studies of the combined approach are all promising with respect to this revamped approach to myocardial reperfusion.74–77 The low-dose fibrinolytic component may be especially helpful in catheter-based reperfusion to more directly address the red, fibrin-rich clot component that otherwise may be part of the embolic burden to the microvasculature.

Conclusions

Through the development of new imaging modalities and specific therapeutics that serve as probes, microvascular obstruction, owing to embolization, has become increasingly recognized as an important sequela of atherosclerotic vascular disease. It is likely that all patients undergoing revascularization, be it surgical or percutaneous, experience embolization. Furthermore, clinical presentation of patients with acute vascular occlusion or ischemia may be the signal that there has already been embolization. Certain therapies routinely used to achieve reperfusion, such as fibrinolitics or transcatheter recanalization, have the potential to induce or augment microvascular obstruction. Underlying inflammation and friability of the diseased arterial segment undoubtedly play a key triggering role. Although recent data have propelled embolization to the pathophysiological forefront in atherosclerotic acute ischemic disease states, considerable investigative work is necessary to prevent or favorably modulate this process. Recognition of the pivotal importance of microvascular obstruction should facilitate integrated fundamental and clinical science to enhance the therapeutic armamentarium in the next century of managing atherosclerotic vascular disease.

References


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