The aggressive treatment of acute myocardial infarction

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NOT SINCE Herrick's description of acute myocardial infarction (AMI) have so many options been available for the treatment of this condition. For decades management of AMI consisted of bed rest, oxygen, prevention of thromboembolic complications, and treatment of arrhythmias and heart failure. Despite the marked reduction of mortality consequent to primary arrhythmias, AMI remains the most common cause of in-hospital death in industrialized nations and both mortality rates and morbidity in survivors are acceptably high. Recently, a number of aggressive therapies designed to reperfuse evolving infarction have been developed. While there is considerable dispute concerning the role that these newer modes of treatment should play in the management of AMI, there is general agreement on the following three basic principles and their corollaries:

1. Mortality of patients after AMI — both early and late — is influenced importantly by the degree of dysfunction of the left ventricle, which in turn is dependent on the size of the initial infarct and on the quantity of myocardium that becomes infarcted later. Therefore, limiting the size of the initial infarct and prevention of subsequent infarction are important goals of efforts to improve patient survival.

2. The time interval between the onset of coronary occlusion and any intervention likely to be successful in limiting the size of the resultant infarct is brief, usually not more than about four hours, and often even shorter. Accordingly, any strategy designed to limit infarct size, if it is to be useful in a large fraction of patients with AMI, must be applied immediately upon the development of symptoms.

3. After infarction some patients remain at high risk of experiencing additional coronary events. Therefore, efforts designed to identify high-risk patients should be made soon after the AMI so that appropriate measures can be taken to reduce the likelihood of subsequent infarction.

The therapy of AMI may, for convenience, be divided into two broad categories — conventional and aggressive; in this discussion, the latter refers to efforts designed to achieve immediate reperfusion of the infarcting myocardium.

Conventional therapy

Conventional therapy may or may not include use of pharmacologic agents such as adrenergic blockers and nitrates to limit infarct size. If the course of the patient with AMI is stable it is desirable before hospital discharge to determine whether provokable ischemia is present, since the latter signifies that the patient is at relatively high risk for reinfarction. Provokable ischemia can be detected by noninvasive stress testing, the use of exercise electrocardiography, thallium-201 scintigraphy, or radionuclide angiography and if it is present, coronary arteriography should ordinarily be carried out to determine whether a large quantity of viable myocardium is perfused by a severely obstructed artery. If so, the patient may be at high risk of losing substantial additional myocardium, and depending on the anatomic findings, mechanical revascularization, either percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG), may be carried out in an attempt to reduce this risk. However, if the patient's condition after conventional therapy for AMI is unstable, i.e., if there is clinical and/or electrocardiographic evidence of recurrent ischemia during early convalescence, coronary arteriography should be carried out immediately to determine if the patient is suitable for early mechanical revascularization.

Thrombolytic therapy

A high percentage of transmural infarctions are caused by occlusive coronary thrombi, and as reviewed elsewhere, immediate thrombolytic therapy is a rational means of achieving early reperfusion (figure

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Several thrombolytic agents are available and these can be administered by either the intracoronary or intravenous routes. Although it has not yet been established unequivocally that thrombolytic treatment is beneficial, there are many suggestions that it may be so. For example, the return of chest pain, electrocardiographic changes, and elevation of levels of cardiac-specific enzymes in some patients after successful thrombolysis suggest that the initial reperfusion limited the evolving infarct.

An improvement in left ventricular function in the patient with AMI whose myocardium has been successfully reperfused has been reported by a number of investigators. However, in the absence of a comparison of treated patients with concurrently randomized control subjects, this finding is only suggestive of a beneficial effect of thrombolytic therapy, since the alterations of left ventricular function that occur without reperfusion during the first few days of AMI are quite variable and spontaneous recanalization is not infrequent. The results to date of controlled randomized trials examining the effect of treatment, rather than of successful reperfusion, on left ventricular function are meager and inconsistent. Evidence is emerging that patients vary in their potential for improvement in left ventricular function after thrombolytic reperfusion. For example, it has been reported that both the global ejection fraction and the contraction of the infarct-related region may not be improved by acute reperfusion in patients with totally occluded vessels and poor or no perfusion of the jeopardized myocardium by collaterals. By contrast improvement in left ventricular contraction after early reperfusion occurred in patients with subtotally occluded arteries or extensive collaterals to the ischemic myocardium.

There is little agreement concerning the effects of thrombolysis on patient survival. Several controlled trials have shown no effect on mortality, but the power of these studies was limited by their small size. One moderate-sized trial, the Western Washington Thrombolytic Trial, did show improved initial survival in patients treated with intracoronary streptokinase (SK), but with the passage of time the difference between treated and untreated groups has become of borderline significance.

Conventional thrombolytic agents (SK and urokinase), when administered intravenously or even by the intracoronary route, produce a systemic lytic state with its attendant dangers of hemorrhage. Tissue-type plasminogen activator (t-PA), which can now be prepared by recombinant techniques (rt-PA), and two other drugs, acyl SK and pro-urokinase, may be capable of inducing thrombolysis without causing a severe systemic lytic state. The efficacy of these new drugs in causing and maintaining coronary arterial patency and their greater safety than conventional thrombolytic agents still remain to be demonstrated in a sizable number of patients: rt-PA and acyl SK are currently under active clinical investigation and early results are encouraging.

It is logical to inject the thrombolytic agent directly into the occluded vessel so that it achieves maximal concentration at the coronary thrombus. However, if coronary thrombolytic therapy is to be successful, it must be carried out immediately upon the patient’s presentation to the hospital, and if an institution wishes to offer its patients intracoronary thrombolytic therapy, a skilled catheterization team and a catheterization-angiographic laboratory must be available on a twenty-four hour a day, seven day a week basis. This is a formidable logistic proposition that is extremely expensive, both in human and material resources. However, even if the personnel and facilities were avail-
able, because of the time required for coronary arterial catheterization, a substantial additional quantity of myocardium can become necrotic between the patient’s initial presentation and the onset of the infusion of the thrombolytic agent into the occluded coronary artery.

To overcome these problems associated with intracoronary thrombolytic therapy, large doses of intravenously administered thrombolytic agents have been used, an approach that has a number of advantages over intracoronary administration. First, since treatment can be begun earlier, often in an emergency room, ambulance, or even in the patient’s home, precious time during which ischemic myocardium becomes necrotic could theoretically be saved and if thrombolysis were achieved promptly, a greater quantity of myocardium might be salvaged. Second, a catheterization team and laboratory are not required for the intravenous administration of a thrombolytic agent, making this form of therapy suitable for any medical care institution and greatly reducing the cost of therapy. Third, the risk to the patient is probably reduced in comparison to intracoronary thrombolysis, since coronary arteriography during the course of AMI is not involved. However, it is likely that the efficacy of intravenous SK in achieving reperfusion may prove to be considerably lower than that of intracoronary therapy. Also, the optimal dose of intravenous SK — perhaps as high as 1.0 to 1.5 × 10⁶ IU — causes a more severe systemic lytic state, presumably with greater risk of hemorrhage, than the smaller doses of SK required for intracoronary administration. However, the intravenous administration of a fibrin-specific thrombolytic agent, such as t-PA, may overcome the latter disadvantage.

After the administration of the lytic agent, regardless of the specific agent or route of administration employed, several therapeutic options are available (figure 1). The most conservative consists of clinical observation and treatment with anticoagulants and antiplatelet agents. If the patient’s condition remains stable without the recurrence of ischemia, as reflected in the development of angina and/or electrocardiographic changes, conventional treatment is undertaken, i.e., after approximately 8 to 10 days an attempt is made by noninvasive methods to detect provokable ischemia and coronary arteriography is carried out only if the latter is present; this may be followed by mechanical revascularization, i.e., PTCA or CABG, depending on the anatomic findings.

After successful thrombolysis, residual high-grade obstruction often persists at the site of the previous occlusion and may be responsible for continued myocardial ischemia and/or coronary reocclusion. Therefore, in patients who are clinically unstable and who exhibit continuing evidence of myocardial ischemia after successful thrombolysis, early mechanical therapy, generally PTCA, is indicated. A number of cardiologists routinely perform PTCA immediately after thrombolysis if severe coronary arterial narrowing persists, even in patients without recurrent ischemia, because of the fear of early reocclusion. The fraction of patients with AMI treated successfully with thrombolytic agents who are suitable for definitive therapy with PTCA may actually be higher than that of patients with chronic stable angina pectoris, since a larger fraction, approximately half, have proximal one-vessel coronary artery disease. PTCA performed shortly after thrombolysis may also be a logical preliminary step in the long-term management of patients with multivessel disease who will be treated subsequently with elective CABG, since the dilation of the most critical stenosis may reduce the risk of preoperative reinfarction.

**Primary angioplasty**

Emergency penetration of a thrombus by a guidewire followed by PTCA may also be used as the primary approach to reperfusion of the myocardium in patients with AMI without preceding thrombolysis. Primary PTCA can result in a high incidence of reperfusion, is relatively safe in skilled hands, and offers a number of potential advantages over thrombolysis:

1. When successful, the severe residual coronary stenosis commonly observed after successful thrombolytic therapy does not occur.
2. After primary PTCA the incidence of total reocclusion may be lower than after thrombolytic therapy alone, although the patient is still at risk of restenosis.
3. In patients with thrombotic coronary occlusion angioplasty can often be accomplished more rapidly and with lower balloon pressures than in patients in whom the procedure is carried out for chronic angina.
4. Primary PTCA avoids the hemorrhagic complications of thrombolytic therapy.
5. This procedure may be ideal for patients with AMI and subtotal coronary occlusion without coronary thrombosis.

The patient whose condition remains stable after successful emergency primary PTCA, like the patient treated by means of thrombolysis, may initially be treated medically and then by further mechanical revascularization if provokable ischemia is present and the anatomic findings are appropriate (figure 1). However, in patients who are unstable and who demonstrate continued ischemia, a thrombolytic agent may
be administered by the intracoronary route if a residual thrombus persists after PTCA, or the patient may be considered for immediate CABG if the coronary anatomy is suitable.

Surgical revascularization

Emergency CABG is the third method that has been used to restore reperfusion in patients with coronary occlusion and AMI\(^1\)\(^2\) (figure 1). This approach also has several potential advantages: (1) In addition to abolishing the obstruction responsible for the acute event and thereby potentially limiting infarct size, CABG offers more definitive treatment than thrombolysis or even PTCA, since other severe obstructions in the coronary vascular bed, which occur in almost half of all patients with AMI and which subsequently may cause ischemia or infarction, may be corrected. (2) In patients with AMI who have multivessel disease, the development of hypotension may cause ischemia and impaired contraction of segments of myocardium at a distance from the infarct, thereby aggravating hypotension, resulting in a vicious cycle. By preventing ischemia of such areas, surgical revascularization may improve pump failure and thereby interrupt this cycle. (3) CABG may be the only means of relieving a critical residual coronary stenosis in patients in whom thrombolysis and/or PTCA have failed, although the time available for such a sequential approach is limited. It may also be employed following successful thrombolysis in patients with critical residual obstruction. While major emergency surgery in the presence of a systemic lytic state is undesirable, it is likely to be safer after t-PA than SK. (4) CABG, like PTCA, may be particularly effective in those patients with AMI without total thrombotic occlusion of the infarct-related artery on coronary arteriography. (5) Surgical revascularization may be the treatment of choice for patients who exhibit an unstable course or provokable ischemia after thrombolysis and who have diffuse, complex, multiple, or distal lesions that are not suitable for PTCA. (6) PTCA, whether carried out for AMI or for chronic or unstable angina, may cause accidental coronary occlusion and CABG may be the only means by which AMI can be averted.

Conclusions

The feasibility of reperfusing infarcting myocardium by three methods — thrombolysis, PTCA, and CABG — has been demonstrated repeatedly; however, the feasibility of use of these techniques does not imply that they should be employed routinely, since their beneficial effects have not been definitively demonstrated. Therefore, it is essential to determine as soon as possible whether or not early reperfusion of evolving infarction actually improves short- and long-term survival, ventricular performance, and the patient’s clinical state. The finding of improved survival and/or left ventricular function in patients whose myocardium were successfully reperfused, while suggestive of a favorable effect, cannot be accepted as firm evidence that thrombolytic therapy is beneficial, since failure of thrombolysis might be coincidental with, rather than responsible for, a poor outcome. In evaluating the effectiveness of coronary thrombolytic therapy, outcome should be compared between treated and untreated patients rather than between patients in whom arterial patency has been achieved and those in whom it has not.

Before recommending thrombolytic therapy for the routine treatment of AMI, not only should beneficial effects be demonstrated unambiguously, but it would also be desirable to demonstrate that the beneficial effects are coherent: i.e., if thrombolysis reduces mortality and if it is hypothesized that this results from an improvement in, or less deterioration of, left ventricular function, then any reduction of observed mortality should be associated with an improvement in left ventricular function. In this regard, it should be noted that the initial improvement in survival noted in SK-treated patients in the aforementioned Western Washington Trial was not accompanied by smaller infarcts or by improved left ventricular function.\(^3\)

Even if early reperfusion with intracoronary thrombolytic therapy were demonstrated to be beneficial and coherent, it must be recognized that this method of treatment is not applicable to the great majority of patients. At the present time our medical care system will not allow more than perhaps 10% or 15% of patients suffering from AMI to be brought to a well-staffed and equipped cardiac catheterization laboratory or operating room in the requisite time, which is usually considered to be less than four hours after the onset of the clinical event. Even if our medical transport system were to be improved so that most patients with AMI could reach a hospital within such a time interval, thousands of new catheterization laboratories would have to be established to make emergency intracoronary thrombolytic therapy available to the bulk of the population experiencing an AMI. The cost of developing such facilities and the training of the personnel required to staff them is so high as to be impractical. Therefore, intracoronary thrombolytic therapy, even if proven to be beneficial, will, for the foreseeable fu-
ture, be limited to a small fraction of patients with AMI.

A major limitation of emergency PTCA, like that of intracoronary thrombolytic therapy, is that a skilled team and fully staffed and equipped catheterization laboratory must be available around the clock. Furthermore, at this time only a limited number of operators have the technical skill and experience required to perform emergency PTCA at relatively low risk to patients with AMI.

The issues surrounding emergency CABG are even more complex. Not only is successful surgical revascularization of patients with AMI possible, but in some instances, the mortality after surgical revascularization has been lower than after medical treatment of AMI, and improvement in hemodynamics after operation has been described. However, as is the case for other means of achieving reperfusion, the timing of CABG is critical. The results in patients operated upon less than four hours after the onset of chest pain are better than in those in whom it is carried out later; mortality actually appears to be increased when surgery is delayed beyond six hours. A major difficulty with analyzing the results of CABG in AMI is that comparisons have been made only between surgically treated patients and nonrandomized control subjects who received traditional medical therapy. Since a prospectively designed randomized trial comparing surgical and nonsurgical treatment has not yet been carried out, the interpretation of the available results has been questioned. There is concern about the complexity and even the feasibility of such a randomized trial, and to the author’s knowledge none is being carried out or is in the active planning stage.

The logistic and economic difficulties that apply to intracoronary thrombolysis and emergency primary PTCA are greater by an order of magnitude with CABG. It is far more expensive to have operating rooms, heart-lung machines, cardiovascular surgeons, cardiopulmonary bypass technicians, operating room nurses, etc., available daily and around the clock, than it is to have catheterization laboratories and coronary arteriographers, or even coronary angioplasters standing by. Almost regardless of its efficacy, emergency CABG may not be widely applicable as therapy for AMI since our health care delivery system would be severely strained by the need to deliver this form of treatment to even a small fraction of patients with AMI.

In contrast to the aforementioned invasive techniques for achieving reperfusion, intravenous thrombolytic therapy can probably be applied within four hours of the onset of the event in the majority of patients who suffer an AMI. Since the treatment can be applied in an emergency room, ambulance, physician’s office, or other ambulatory health facility, or even in the patient’s home, it can fit realistically into our medical care system and may turn out to be, at the least, an effective holding maneuver in many patients. Therefore, it is critical from the public health point of view, to determine the efficacy of this therapy. Since reocclusion may occur in a significant number of patients treated by this technique, the option of transferring them expeditiously to an institution where their coronary anatomy can be assessed and where, if necessary, mechanical reperfusion can be carried out, should be available.

The successful early reperfusion of evolving infarction could lead to a major reduction in this important cause of death. However, the availability of the several methods of achieving reperfusion also poses a number of problems. First, there is a hazard of adopting by common consent a therapeutic approach primarily because it is intuitively sensible, before its effectiveness has been firmly established; second, there is the danger of doing too much, particularly to patients with small, uncomplicated inferior wall AMIs in whom the prognosis is excellent; third, it is possible that many patients who have already completed their infarction and who therefore cannot benefit from reperfusion will be treated unnecessarily; and finally, the widespread use of invasive methods of reperfusion may tax further a medical care system that is already under severe constraints. The argument, therefore, is compelling for concentrating efforts on carefully controlled trials of the efficacy of the early intravenous administration of the most effective available thrombolytic agent(s), since this appears to be the only approach to reperfu-bring infarcting myocardium that can be applied in the majority of patients with evolving AMI.

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