More than 20 years of misconceptions derailed acceptance of reperfusion therapy for acute myocardial infarction (AMI). Cardiologists abandoned reperfusion for AMI using fibrinolytic therapy, explored in 1958, because they no longer attributed myocardial infarction to coronary thrombosis. Emergent aortocoronary bypass surgery, pioneered in 1968, remained controversial because of the misconception that hemorrhage into reperfused myocardium would result in infarct extension. Attempts to limit infarct size by pharmacotherapy without reperfusion dominated research in the 1970s. Myocardial necrosis was assumed to progress slowly, in a lateral direction. At least 18 hours was believed to be available for myocardial salvage. Afterload reduction and improvement of the microcirculation, but not reperfusion, were thought to provide the benefit of streptokinase therapy. Finally, coronary vasospasm was hypothesized to be the central mechanism in the pathogenesis of AMI. These misconceptions unraveled in the late 1970s. Myocardial necrosis was shown to progress in a transmural direction, as a “wave front,” beginning with the subendocardium. Reperfusion within 6 hours salvaged a subepicardial ischemic zone in experimental animals. Acute angiography provided in vivo evidence of the high incidence of total coronary occlusion in the first hours of AMI. In 1978, early reperfusion by transluminal recanalization was shown to be feasible. The pathogenetic role of coronary thrombosis was definitively established in 1979 by demonstrating that intracoronary streptokinase rapidly restored flow in occluded infarct-related arteries, in contrast to intracoronary nitroglycerine which rarely did. The modern reperfusion era had dawned. (Am Heart J 2015;170:971-980.)

The path from Herrick’s seminal observation in 1912 that acute myocardial infarction (AMI) is caused by coronary thrombosis to the use of thrombolytic therapy and primary percutaneous intervention (PCI) was anything but direct. A series of misconceptions delayed the acceptance and implementation of reperfusion therapy by more than 20 years.

Coronary thrombosis was thought to be a consequence, rather than the cause of AMI

Extensive research led to universal acceptance of the causative chain of plaque rupture, occlusive coronary thrombosis, and myocardial necrosis by the 1930s. In 1958, Fletcher et al administered intravenous streptokinase to 24 patients with AMI in their initial evaluation of a “sustained thrombolytic state,” in hope of reducing infarct size by “the rapid dissolution of a coronary thrombus.” They reported early peaking of serum transaminase as an indirect sign of reperfusion. Their study marked the beginning of reperfusion therapy for AMI. However, when the Food and Drug Administration (FDA) approved fibrinolytic therapy for several thromboembolic conditions in 1977, AMI was not among them. Sherry, himself said, “Cardiologists no longer stressed coronary thrombosis as the cause of acute infarct.” The first misconception had taken hold.

Beginning in 1956, some pathologists reported a low prevalence of coronary thrombi in “fatal infarcts” and questioned their causative role. Roberts attributed myocardial necrosis to a mismatch between myocardial oxygen supply and demand, which could be easily triggered in patients with severe chronic coronary artery disease who have completely lost their coronary reserve. Coronary thrombi, found primarily in patients who had died of pump failure, were thought to have developed after the onset of infarction due to “a markedly diminished cardiac output and the consequent slow down of coronary blood flow” in vessels with severe chronic plaques. Total occlusion by such thrombi was considered to be pathogenetically irrelevant, such that their lysis would not be useful.
These hypotheses were controversial among pathologists and remained so at a 1973 National Institutes of Health workshop.1,2 Clinicians, however, were greatly influenced by a study from the Coronary Care Unit of the Karolinska Institutet in Stockholm, Sweden. Radioactive fibrinogen administered to patients with AMI was found to be incorporated into the entire coronary thrombus in nonsurvivors, seemingly supporting the view that myocardial infarction occurs first and thrombus formation is a secondary event.10 Many cardiologists embraced this reversal of the cause and effect relationship between coronary thrombosis and myocardial necrosis and abandoned the reperfusion concept.5

Reperfusion was thought to cause infarct extension

Although fibrinolytic therapy was temporarily abandoned, cardiac surgeons, following their pioneering work at the Cleveland Clinic in 1968, Favaloro et al11 explored reperfusion by aortocoronary bypass surgery (CABG) throughout the 1970s, albeit with contradictory results. The poor outcomes reported by some centers12 and detrimental effects of reperfusion described in experimental animals gave rise to the second misconception: that reperfusion causes metabolic derangements and infarct extension by hemorrhage into the reperfused myocardium with hemodynamic deterioration, often resulting in either shock or fatal arrhythmias.13,14 The surprisingly low hospital mortality rates reported by some centers performing emergency CABG within 6 hours of infarct onset were inconsistent with this view.15,16 but reperfusion by acute CABG was never assessed in a randomized trial. “Thus, presently available information does not justify emergency revascularization as treatment for AMI…” was the textbook conclusion in 1980.17

Pharmacotherapy was thought to salvage myocardium in the absence of reperfusion

Braunwald et al18 observed a decrease of ischemic ST elevations in the distribution of ligated coronary arteries when they reduced myocardial oxygen consumption in experimental animals. In 1969, they hypothesized that “reduction of myocardial oxygen demands …may reduce … the size of the infarction.” This concept initiated a search for “anti-infarct drugs,” Hearse’s19 label for those agents presumed to limit infarct size in the absence of reperfusion. β-Adrenergic blocking agents were first proposed followed by nitrate preparations and other vasodilators, glucose-insulin-potassium solutions, anti-inflammatory drugs, and surprising choices such as cobra venom, rutoses, and hyaluronidase.19,20 During the 1970s, approximately 50 anti-infarct drugs were reported to limit infarct size in the absence of reperfusion in experimental animals.19 The positive results of subsequent clinical pilot studies fostered enthusiasm and prompted Braunwald and Maroko21 to call for a “careful, rigorously conducted prospective trial.”

The Multicenter Investigation of the Limitation of Infarct Size (MILIS), a randomized, blinded prospective trial initiated by the National Heart, Lung, and Blood Institute in 1977, assessed the efficacy of propanolol and hyaluronidase in patients with evolving infarction presenting within 18 hours of symptom onset. Both agents had been promising in animal models and clinical pilot studies, but they failed to decrease infarct size in the MILIS trial.22,25

The Animal Models for Protecting Ischemic Myocardium (AMPIM) trial organized by the National Heart, Lung, and Blood Institute in 1978 standardized canine models of myocardial infarction.24 It evaluated the efficacy of verapamil and ibuprofen “because these drugs … with presumably different mechanisms of myocardial protection … had previously shown considerable promise as possible therapies to limit infarct size.” Neither drug, however, altered infarct size in the AMPIM trial. The trial showed instead that previous animal studies had been undersized; failed to control for baseline variables, most importantly collateral flow; and often used flawed methodology to assess infarct size.24

Thus, appropriately designed trials refuted the positive findings from initial animal and clinical studies. Eventually, better models demonstrated that, even at a low metabolic rate, energetic overspending results in inevitable cell death if flow is not restored.25 Although no agent ever achieved clinical acceptance as an anti-infarct drug,19 the methods developed to assess infarct size20 and the scientific rigor in testing this hypothesis22-24 informed the reperfusion studies to come.

The survival benefit of streptokinase was thought to result from fibrinogenolysis rather than fibrinolysis

Whereas in the United States, Fletcher’s and Sherry’s feasibility study was followed by only one small randomized trial of streptokinase therapy in AMI,26 20 such trials were conducted in Europe and Australia during the 1960s and 1970s.27 The presumed benefit of streptokinase tested in these trials, however, was not reperfusion by lysis of thrombus-bound fibrin, but rather cleavage of circulating fibrinogen by plasmin, a reaction described in 1945.28 Fibrinogenolysis with streptokinase was shown to reduce blood viscosity,29 peripheral vascular resistance, afterload, and thus myocardial oxygen demand.30 A second proposed mechanism targeted microthrombi in the arterioles and venules surrounding the necrotic area which could be dissolved rapidly with streptokinase in an animal model.31 It was hypothesized that these microthrombi cause infarct extension by impairing collateral flow. A 12- to 72-hour
infusion of streptokinase was proposed to restore the microcirculation and thus limit or even prevent infarct extension. This regimen was used in the European and Australian streptokinase trials.27 As late as 1979, the significant survival benefit from a 12-hour intravenous streptokinase infusion found in the European Cooperative Trial was attributed solely to afterload reduction and improved microcirculation. Reperfusion was not even considered.32

The reperfusion concept resurfaced for a brief moment in the Soviet Union in 1976, when Chazov et al33 reported reflow in 1 of 2 patients treated with an intracoronary infusion of fibrinolysin. Written in Russian, this case report remained unknown outside the Soviet Union for years. Chazov did not pursue this approach further. Instead, 1 year later, he coauthored a pilot study using hyaluronidase, an anti-infarct drug without reperfusion.34

Coronary vasospasm was thought to have a central role in the pathogenesis of AMI

In 1977, Oliva and Breckinridge35 reported reperfusion in 6 of 15 patients with AMI after the intracoronary administration of nitroglycerin, suggesting that coronary artery spasm led to total occlusion. The authors hypothesized that spasm might be caused by platelet aggregation at a severe atherosclerotic lesion with release of vasoactive substances. Aggregation of platelets at the site of severe coronary stenoses causing intermittent complete occlusion had been demonstrated in a canine model by Folts et al36 1 year earlier. Oliva and Breckinridge citing this study hypothesized that persistent spasm was the primary event in AMI. Neither plaque rupture nor an oxygen supply/demand mismatch due to a loss of coronary reserve would play a role in the pathogenesis of AMI according to this hypothesis.

Progression of myocardial necrosis was thought to be slow and follow a bull’s-eye pattern

Using histochemical staining techniques, Cox et al37 had concluded in 1968 that myocardial necrosis does not begin until 6 hours after coronary ligation in the center of an enlarging ischemic area in which myocardial oxygen supply was assumed to be borderline. Necrosis was thought to expand laterally in concentric rings (a “bull’s-eye” pattern), eliminating the entire ischemic area, only after more than 18 hours of coronary occlusion. These studies led cardiologists and cardiac surgeons alike to believe, through the 1970s, that at least 18 hours was available for limitation of infarct size and improvement of survival by ameliorating the mismatch between myocardial oxygen demand and supply in an ischemic “twilight” zone.11,18,22,25,38

Myocardial necrosis progresses rapidly in a “wavefront” pattern

A correction of these misconceptions began with canine studies published by Schaper and Pasyk,39 Hirzel et al,40 and Reimer et al41,42 between 1976 and 1979. Myocyte necrosis was shown to progress from subendocardium toward epicardium in a wavefront pattern, following a transmural gradient of collateral flow. A subepicardial, not lateral, zone of ischemic but viable myocardium was found to be available for salvage by reperfusion for 3 to 6 hours at most. Microvascular injury was shown to progress at a slower rate than does myocyte necrosis. Reperfusion-related myocardial hemorrhage, which was always confined to the subendocardial area of microvascular injury, did not increase infarct size.41 Life-threatening reperfusion arrhythmias were noted to become less frequent with transmural progression of myocardial necrosis, rarely occurring after 3 hours.42 A time frame of 3 to 6 hours for myocardial salvage would severely limit the clinical applicability of reperfusion therapy; however, occlusive thrombi tend to develop in a “protracted, recurring course,” a process quite different from the abrupt ligation of a normal coronary artery in the dog model, and ischemic symptoms frequently begin before coronary occlusion is complete, as first shown by Sinapius8 in 1965. Furthermore, residual flow-through collaterals delayed the onset and progression of the wavefront of ischemic cell death in dog models.39,42 Based on these data, patients were enrolled up to 12 hours after symptom onset in a surgical reperfusion study at the University of Göttingen, Germany, headed by one of the authors (K.P.R.). In subsequent studies of mechanical transcatheter recanalization and intracoronary streptokinase, these investigators maintained the 12-hour limit, whereas others adopted time frames ranging from 4 to 24 hours after symptom onset. Large trials eventually established that reperfusion therapy is most efficacious within 3 or 4 hours of symptom onset, but may confer clinically meaningful benefit up to 12 hours in selected patient subsets.45

Acute coronary angiography reveals high incidence of total thrombotic coronary artery occlusion, and rapid reperfusion by transluminal recanalization is shown to be feasible, possibly preserving function

In the late 1970s, in vivo evidence of the high incidence of total coronary occlusion in the initial hours of AMI became available, when the groups in Spokane, Washington, and Göttingen, Germany, analyzed coronary angiograms performed before emergency coronary artery
bypass surgery.\textsuperscript{15,44} In all nonsurviving Göttingen patients with total occlusion of the infarct-related artery at angiography, Sinapius demonstrated a thrombus attached to a fissured plaque, whereas in those with subtotal occlusion, there was a ruptured plaque with subintimal thrombus (Figure 1).

On June 13, 1978, a patient in Göttingen with unstable angina developed an acute inferior wall infarction during coronary angiography, the severe right coronary artery (RCA) lesion having progressed to total occlusion. Because standard medical therapy including reduction of myocardial oxygen consumption with nitroglycerin brought no relief and immediate bypass surgery was not available, a novel therapeutic maneuver to achieve rapid reperfusion was used for "compassionate use."\textsuperscript{46} A standard 0.032-inch guide wire was used to push the presumed catheter-related thrombus downstream.\textsuperscript{46} Flow was restored, and symptoms and electrocardiogram (ECG) changes resolved immediately (Figure 2). Bypass surgery was performed several hours later. Necrosis was negligible, probably as a result of rapid transcatheter reperfusion prior to surgical revascularization with its inevitable delays.

Subsequently, "transluminal recanalization," a catheter-based technique introduced by Dotter and Judkins\textsuperscript{47} for the recanalization of occlusions in the arteries of the leg, was modified by one of the authors (K.P.R.).\textsuperscript{48} The initial intracoronary technique used 0.032- or 0.038-inch guide wires, specifically manufactured by Cook for this purpose, which differed from standard coil-spring guide wires by their long, floppy, shapeable tips (Figure 3). A later technique used a prototype 0.018-inch guide wire over which a recanalization catheter with a tapered tip was advanced to compress the thrombus against the vessel wall (Figure 4). This system appeared safer than Grüntzig’s prototype balloon catheters because of its greater steerability. Transluminal recanalization was attempted in a proof of concept study of 15 patients...
with spontaneous infarctions within 6.6 hours of symptom onset. Reflow was achieved in 9 patients and recovery of left ventricular function was documented. In contrast, left ventricular function deteriorated in a historical control group of 13 patients, although the initially occluded infarct-related artery was open in 5 of these patients at repeat angiography several weeks later. Spontaneous late coronary artery recanalization was recognized to occur commonly (5/13; 38%). Transluminal recanalization in AMI was shown to be feasible, accelerating reperfusion and potentially salvaging myocardium.

**Intracoronary administration of streptokinase versus nitroglycerin reestabishes the role of coronary thrombosis in AMI**

Spontaneous coronary artery recanalization could be attributed to either endogenous thrombolysis or spontaneous resolution of coronary spasm. Occlusive coronary spasm was again proposed as the primary event in AMI by Maseri et al in 1978, citing Oliva’s and Breckinridge’s earlier report of reflow in 40% of patients given intracoronary nitroglycerine. Although mechanical intracoronary interventions could not determine the role of coronary thrombosis or spasm, selective administration of drugs appeared to hold the potential to differentiate between these mechanisms. In a largely ignored 1972 necropsy study, Sinapis had shown that fibrin is the predominant component in 80% of occlusive coronary thrombi and suggested that those would be targets for fibrinolysis, whereas this therapy was likely to fail in the remaining 20%, which consisted primarily of platelets or prolapsed atheromatous material. Intracoronary administration of a fibrinolytic agent had dissolved fibrin-rich coronary thrombi more rapidly than an intravenous infusion in experimental animals. Selective injection of streptokinase into the thrombosed artery of Scribner shunts to restore blood flow had been used extensively. (Chazov’s case report of intracoronary thrombolysis had not yet been translated from the Russian and was not yet part of the knowledge base in the West).

In 1979, the relative roles of coronary artery spasm and coronary artery thrombosis were assessed using intracoronary nitroglycerine and intracoronary streptokinase administration in a trial of 72 patients, 62 with AMI and 10 with preinfarction angina. An initial intracoronary bolus of nitroglycerin was ineffective beyond inducing transient reflow in 6 of 62 patients with AMI. Restoration of normal and sustained flow by an intracoronary streptokinase infusion in 38 (83%) of 46 totally occluded and 5 (31%) of 16 subtotally occluded infarct-related coronary arteries provided definitive in vivo evidence of fibrin-rich intracoronary thrombi. Resolution of ischemic symptoms and ECG changes proved the pathogenetic role of these
thrombi in AMI. Biopsies obtained during subsequent bypass surgery evidenced that reperfusion had limited myocardial necrosis to the subendocardium (Figures 5 and 6). In contrast, failure of both drugs in the subtotal occlusions of the 10 patients with preinfarction angina pointed toward a different pathogenetic mechanism in this syndrome: that is, plaque rupture causing nonocclusive platelet thrombi as first suggested by Sinapius in his 1965 necropsy study. The first report of the pathogenetic role of thrombus in this trial was rejected for the 29th Annual Scientific Session of the American College of Cardiology in March 1980. This Scientific Session was the last to feature drugs not resulting in reperfusion exclusively. A series of publications from Gottingen initiated a reassessment of thrombosis and reperfusion in AMI.

Reperfusion therapy in ST-elevation myocardial infarction is accepted

The annual meeting of the American Heart Association (AHA) in Anaheim, California, in November 1979 was to become a watershed event in the history of reperfusion. In a presentation of the Göttingen experience, a large international audience of cardiologists saw angiograms demonstrating reperfusion by either transluminal recanalization or intracoronary streptokinase infusion (https://youtu.be/uVzysOX-wHc). The immediate alleviation of ischemic pain and ECG changes and subsequent recovery of left ventricular function after reperfusion were reported. This presentation was met with a combination of curiosity and enthusiasm. At the subsequent 1980 AHA meeting, several groups in Europe and the United States reported that they had reproduced these results. Chazov finally translated his 1976 case report and sent emissaries to distribute it to various centers.

In 1980, DeWood et al extended earlier angiographic reports of the high incidence of total coronary occlusion in the first hours of infarction and thrombus retrieval from the infarct-related artery during emergency bypass surgery. By linking these in vivo observations with the ECG changes of ST-elevation myocardial infarction (STEMI), DeWood et al further clarified the role of occlusive coronary thrombosis in this syndrome, an important step in identifying STEMI as the appropriate target for fibrinolytic therapy.

German centers pooled their experience with intracoronary fibrinolysis, which soon was expanded to a
In 1982, after the addition of US centers, the database was large enough to secure FDA approval for intracoronary fibrinolysis to accelerate coronary artery recanalization. Intracoronary streptokinase administration was sometimes combined with mechanical recanalization using guide wires, either to accelerate reperfusion as in the first reported case (Figure 5) or because of streptokinase failure, which was attributed to a predominance of platelets in the occluding thrombus. In 1983, Hartzler et al. reported treatment of such lysis-resistant thrombi with angioplasty balloons, achieving not only reperfusion but also a larger lumen by dilating the underlying stenosis. Subsequently, they performed balloon angioplasty of totally occluded infarct arteries without antecedent fibrinolytic therapy. The success rate of 94% in 500 consecutive cases with AMI, which Hartzler’s group reported after steerable balloon systems became available, far exceeded reperfusion rates of fibrinolysis and inspired wide interest in this modality.

Randomized trials were begun as early as 1981. Khaja et al. and the University of Michigan Reperfusion group demonstrated that reperfusion is achieved more readily with intracoronary streptokinase than with placebo infusion. In the first Mount Sinai/NYU Reperfusion Trial 74% (32/43) of totally occluded infarct-related arteries were acutely recanalized with intracoronary streptokinase, whereas only 6% (1/18) had flow restored with an intracoronary infusion of nitroglycerine. This confirmed that the only useful pharmacologic strategy for coronary artery recanalization during interventional angiography is lysis of an occlusive thrombus by administration of a thrombolytic agent. A significant survival benefit of intracoronary streptokinase therapy was documented in The Western Washington Trial under the leadership of Kennedy et al. The complete sequence—reperfusion by intracoronary streptokinase (preceded by intravenous streptokinase in a subgroup), reduction of infarct size, preservation of left ventricular function, and improved survival—was documented in a trial organized by the Interuniversity Cardiology Institute in the Netherlands. Schröder et al. and Neuhaus et al. developed a simplified, accelerated regimen of intravenous streptokinase, achieving rapid reperfusion in 50% to 60% of patients. These studies set the stage for the Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto Miocardico (GISSI) trial, which, published in 1986, initiated the era of “Mega Trials” in cardiology. Its finding of a highly significant 18% survival benefit in patients with STEMI treated with streptokinase established the validity of the reperfusion concept once and for all.
This was reflected in the FDA approval of the use of streptokinase “when administered by either the intravenous or intracoronary route ... for the lysis of intracoronary thrombi, the improvement of ventricular function, and the reduction of mortality associated with AMI” in November of 1987. Recombinant tissue plasminogen activator was approved shortly thereafter. The 1990 American College of Cardiology/AHA guidelines for the early management of patients with acute myocardial infarction recommended intravenous thrombolysis as “the first line of therapy.”

Primary balloon angioplasty, when compared with intracoronary streptokinase, achieved not only significantly larger lumina but also greater recovery of left ventricular function and less peri-infarct ischemia in a 1986 study. When compared with intravenous fibrinolytic therapy, primary PCI resulted in superior clinical outcomes in trials published by Grines et al, Gibbons et al, and Zijlstra et al in 1993 and in 2003 meta-analysis of 23 randomized trials by Keeley et al. The current American College of Cardiology/AHA and European Society of Cardiology guidelines for the management of patients with ST-elevation myocardial infarction recommend primary PCI as “the preferred reperfusion strategy for patients with STEMI.”

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Appendix A. Supplementary data
Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ahj.2015.08.005.

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