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The Open Artery Hypothesis

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ABSTRACT

There is considerable clinical and experimental evidence of the benefit of late reperfusion of infarct-related arteries, referred to as the open artery hypothesis, in patients with acute myocardial infarction who presented too late to salvage at-risk ischemic myocardium. In addition to myocardial salvage, reperfusion of the infarct-related artery prevents infarct expansion, reduces development of ventricular remodeling, and decreases ventricular arrhythmia. The Occluded Artery Trial recently answered a major question related to the open artery hypothesis in a high-risk, asymptomatic patient with an occluded infarct artery. In this review, clinical and experimental evidence of the benefit of the open artery hypothesis will be discussed. **(Korean Circulation J 2007;37:235-243)**

KEY WORDS : Myocardial infarction ; Reperfusion ; Ventricular remodeling.

Introduction

For two decades, a variety of indirect evidence has indicated the benefit of late reperfusion of the infarct-related artery(IRA) in patients with acute myocardial infarction(AMI), known as the "open-artery hypothesis".[1-4] The most important treatment mission for AMI is early reperfusion for salvaging ischemic myocardium and preserving ventricular function. Early reperfusion has been found to improve short-term and long-term survival rates.[5] Therefore the phrase "time is muscle" is an aphorism that is well-known to cardiologists.

Observational studies, however, revealed that patients with patent IRA after AMI showed less dilatation of the ventricles and survived longer than those who had occluded IRA.[5-12] The mechanism of beneficial effects of early reperfusion is not simple as it was first thought to be. The degree of the treatment effect was larger than the degree of ventricular function improvement due to myocardial salvage at risk area.[1)2)] In addition to myocardial salvage, reperfusion prevents infarct expansion, reduces development of ventricular remodeling, and decreases ventricular arrhythmia.[1-4] Even though late reperfusion could not reduce infarct size, clinical benefit is offered by the other mechanisms.[1-4] At this point, the open artery hypothesis is the clinical background for the revascularization of occluded IRA in otherwise stable patients.

Recently, the Occluded Artery Trial(OAT)[13] answered the question of whether routine percutaneous coronary intervention (PCI) days to weeks after AMI improved long-term clinical outcomes in asymptomatic high-risk patients with an occluded infarct artery. This clinical result might change the treatment guidelines for AMI. The purpose of this review is to discuss the clinical and experimental evidence of the benefits of the "open-artery hypothesis".

The "Open-artery Hypothesis"

The salvage of ischemic myocardium by reperfusion therapy represents a major advance in the management of AMI. Reperfusion was studied in canine models. Reimer et al.[14] and Reimer and Jennings[15] demonstrated a wave front of myocardial necrosis from the endocardium to the epicardial direction by temporary mechanical occlusion of a coronary artery and its subsequent release. The extent of transmural necrosis was 38% after 40 minutes, 57% after 3 hours, 71% after 6 hours, and 85% after 24 hours of coronary artery occlusion followed up by reperfusion.[14] The infarct size was significantly smaller in the 40-minute and 3-hour reperfusion group compared with the dogs undergoing reperfusion after 24 hours of occlusion.[14] Six-hour infarcts were of intermediate size, but were not significantly different from either the 3-hour, or 24-

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hour infarcts(Fig. 1).

These studies show a direct correlation between the duration of coronary artery occlusion and the extent of cell necrosis. Thus, reperfusion up to 3 hours and possibly 6 hours from the moment of coronary artery ligation reduces ischemic myocytes, limits infarct size, and thus preserves ventricular function. In 1980, DeWood et al.[16] identified thrombotic occlusion of an epicardial coronary artery as a cause of AMI in patients. Thereafter thrombolytic therapy to restore reperfusion was developed for the reduction of cardiovascular mortality.[17][18] In the thrombolytic era, the benefit was greatest when such therapy was initiated within 1 hour of symptom onset.[17][18]

As believed initially, thrombolytic therapy was to interrupt the progression from myocardial ischemia to necrosis that resulted from thrombotic occlusion of the IRA. This measure would limit the size of the infarct and preserve ventricular function.[19] The ventricular function and IRA patency have been shown to be powerful predictors of early and late outcomes after AMI.[20] The patient survival and ventricular function depend on the time interval between the onset of symptoms and the commencement of treatment.[21-26]

The early reperfusion of an occluded IRA could salvage ischemic myocardium which preserves global ventricular function and improves patient survival. A key aspect of this paradigm is that the opening of the IRA is important. The original "open-artery theory" notion is "time-dependent" effect. The concept that a patent IRA and myocardial reperfusion confer a benefit beyond that resulting from myocardial salvage has given rise to the "open-artery hypothesis".[1][2] This hypothesis includes hemodynamic and clinical benefits both to time-dependent and time-independent effects of coronary artery reperfusion. Cigarroa et al.[6] analyzed retrospectively the course of 179 patients who did not receive thrombolytic therapy after AMI and single-vessel disease. Although the left ventricular volume and global ejection fraction were similar in the two group initially, at a mean follow-up of 47 months, none of 64 patients with partial or complete antegrade blood flow in the IRA had died, compared with 21 deaths among the 115 patients in whom flow in the IRA was absent. In addition, the incidence of congestive heart failure(CHF) was also lower in the patients with patent than in those with occluded IRA (6% versus 17% respectively).

Trappe et al.[7] studied 214 patients with single vessel coronary artery disease, an occluded coronary artery was associated with a much higher incidence of subsequent sudden death than was a patent IRA(15% versus 3% respectively). Pfeffer et al.[8] studied ventricular enlargement after anterior infarction in which baseline assessment of ventricular size was conducted 3 weeks after infarction. They found that total occlusion of the IRA was an important predictor of further ventricular enlargement at 1 year(Fig. 2). In the Survival and Ventricular Enlargement(SAVE) trial,[9] the post-myocardial infarction patency of the IRA was also identified as an independent predictor of a lower incidence of a combined clinical endpoint such as cardiovascular death,

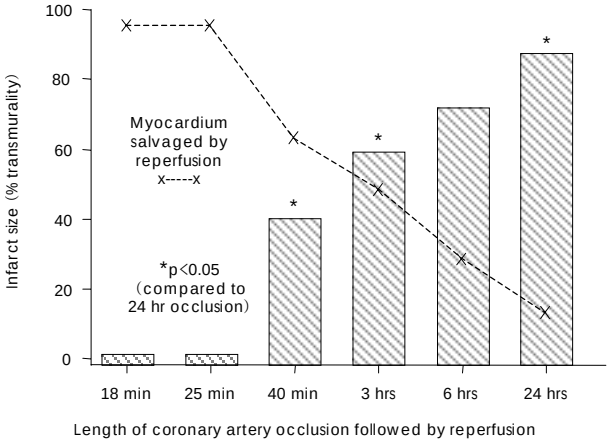

Fig. 1. Temporary circumflex coronary artery ligation and infarct size in a dog. Reperfusion after 18 and 25 minutes represents a period of reversible ischemia in which infarct transmurality is negligible. After 40 minutes, 3 hours, and 6 hours, however, reperfusion results showed a graded and time-dependent limitation of infarct size. The infarct size limitation following reperfusion after 40 minutes and 3 hours is significant compared with prolonged coronary artery occlusion (24 hours).[4]

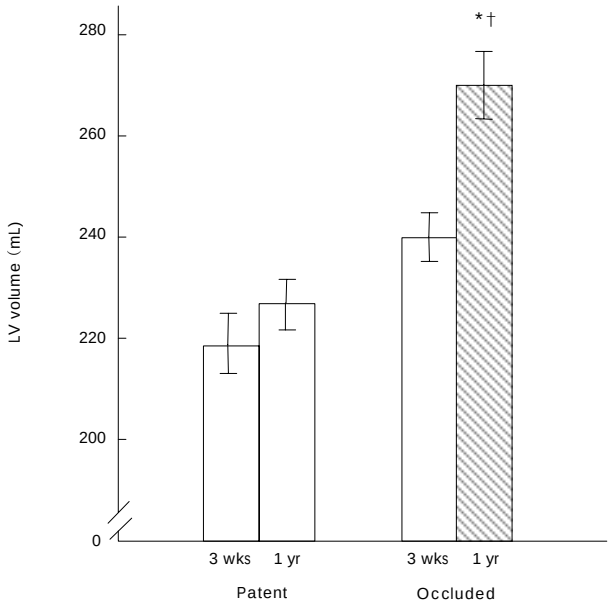

Fig. 2. Bar graph of left ventricular volume as determined by biplane angiography in survivors of first anterior Q wave infarction with paired studies performed at 3 weeks and 1 year after this initial infarction. Patients with a patent left anterior descending coronary artery at the initial catheterization did not demonstrate progressive enlargement over time. In contrast, patients with an occluded vessel supplying their infarcted region showed time-dependent ventricular enlargement; by 1 year (solid bar), these enlargements had increased above their baseline size († $p<0.05$) and had greater volumes (*$p<0.05$) than patients with patent vessels.[10] LV: left ventricle.

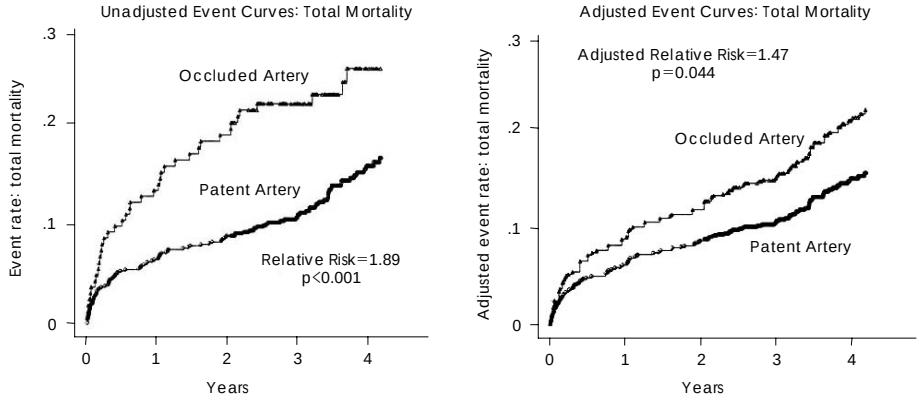

Fig. 3. Univariate survival curves for total mortality by infarct artery patency.[9]

severe heart failure, recurrent infarct, or marked deterioration of the left ventricular ejection fraction(Fig. 3).[9)10)] At an average follow-up of 3.5 years, 37% of the patients with a patent IRA had one of these clinical endpoints, compared with 51% in those with an occluded IRA.

Trials of thrombolysis have also shown that IRA patency correlates strongly with improved survival, both short-term and long-term.[5)] In these trials carried out early in the thrombolytic era, thrombolytic therapy was began relatively late, an average of 4.5 hours after the onset of symptom. Recanalyzation did not occur for another 45 minutes, and it is unlikely that such delayed therapy salvaged much myocardium. Nevertheless, survival correlated with the presence of a patent IRA. The GUSTO-1 angiographic substudy[11)] showed a strong correlation of the 90-minute patency of the IRA with a reduction in mortality rates after AMI. The 30-day mortality rate among patients with complete reperfusion (TIMI-3 flow) was 4.4% and for those with an occluded IRA(TIMI 0-1 flow) was 8.9%. Patients with a partial or incomplete reperfusion had a mortality rate of 7.4%. In addition, the left ventricle(LV) function was better and LV end systolic volume was smaller in patients with TIMI-3 flow compared with those with less TIMI flow grades.[11)] Only early and complete TIMI-3 flow improved the survival rate and LV function. Sustaining the patency of the early open artery is necessary for continued benefit. In the Thrombolysis and Angioplasty in Myocardial Infarction(TAMI) trial. Ohman et al.[27)] noted that the failure to achieve IRA patency, reocclusion, resulted in increased in-hospital mortality rates compared with early and sustained patency(17.2% versus 4.2%). When IRAs became reoccluded after thrombolytic therapy, the failure of angioplasty to restore patency was associated with a higher mortality(26.7%) than in patients in whom mechnical reperfusion was successful(12.1%). Thus, the available evidence clearly supports the notion that early, complete, and sustained reperfusion of the IRA can salvage ischemic myocardium, preserve LV function and improve survival rates. Recently, Roe et al.[28)] suggested that optimal reperfusion should be included adequate microvascular function and myocardial tissue perfusion. TIMI frame count and myocardial blush grade are new angiographic techniques for this purpose.[28)29)]

Ventricular Remodeling

Ventricular remodeling after AMI is a surrogate marker of ventricular dysfunction.[10)30)] Acute morphologic change of the myocardial infarct area called infarct expansion. Hutchins and Bulkley[31)] defined infarct expansion as an acute dilatation of and thinning of the area of the infarction not explained by additional myocardial necrosis. The remote area of ventricular myocardium also changed as compensatory hypertrophy and the ventricular cavity was dilated as the ventricular function deteriorates due to large infarct size, transmural infarct, and some medications such as steroid and nonsteroidal antiinflammatory drugs(Fig. 4).[10)30)32)33)] The ventricular shape changed from ellipsoid to global.[10)30)] Clinical trials showed that ventricular remodeling after AMI is a marker of poor prognosis. In an echocardiographic substudy[34)] of the SAVE trial, a cohort of over 500 patients followed up for a mean of 3 years underwent echocardiographic assessments 11 days and 1 year post-infarction. Regardless of the treatment received, captopril or placebo, patients with end-systolic and end-diastolic left ventricular areas in the upper quartile of the 11-day assessments showed the highest cardiovascular mortality rate(Fig. 5).[34)] Long term, left ventricular volume is a sensitive marker of postinfarction ventricular dysfunction, with left ventricular end-systolic volume being one of the most powerful independent predictors of mortality after myocardial infarction.[20)] Medications[35)36)] to prevent or limit ventricular remodeling improved cardiovascular survival rates and ventricular function in clinical trials of patients with chronic heart failure. Hochman and Choo[37)] and Kim et

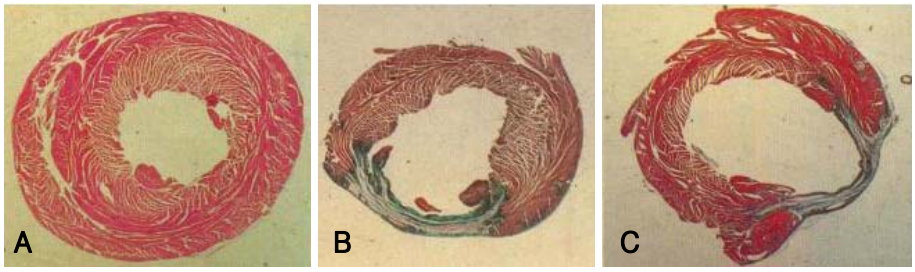

Fig. 4. Photographs of transverse sections of rat left ventricle (LV) subjected to coronary occlusion for 21 days. A: noninfarcted (normal) sham-control rat with normal thickness of the LV wall. B: myocardial infarction without treatment (control), large transmural infarction of the anterior wall showing considerable thinning of the infarct compared with the septal wall and sham-control. The LV cavity was dilated. C: myocardial infarction with 2-(3-benzoyl-phenyl)-propionic acid(ketoprofen) injection. The LV cavity was more dilated than in the control, and the infarct scar is thinner than that of the control (A: hematoxylin-eosin stain, B&C: Masson's trichrome stain).[32]

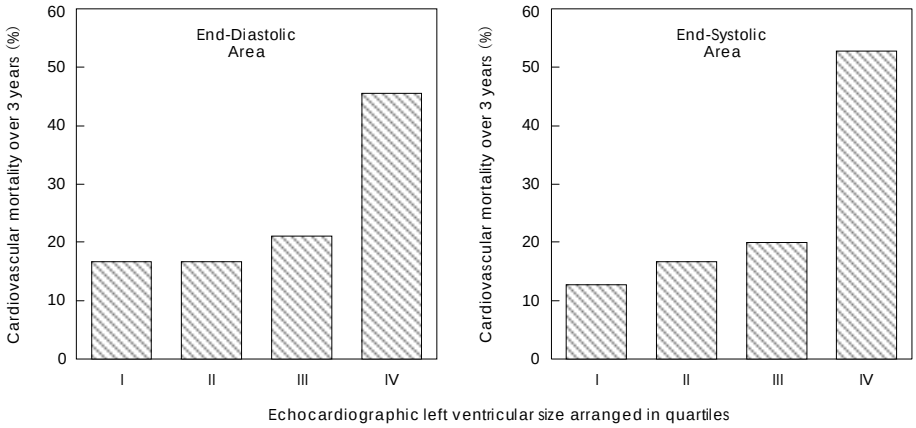

Fig. 5. Baseline left ventricular size and subsequent cardiovascular mortality. Baseline end-diastolic and end-systolic areas measured 11 days post-infarction are represented in quartiles. The figure shows that the 3-year cardiovascular mortality rate was greatest in the patients whose left ventricular size was in the upper quartile early post-infarction.[34]

al.[38] demonstrated that late reperfusion of experimental myocardial infarction in rats even did not reduce infarct size, late reperfusion reduced infarct expansion. Histologic examination of the late reperfusion group exhibited significantly reduced numbers of dead myocytes which suggested an acceleration of cellular clearance and wound healing.[37][38] The late reperfusion group showed increased numbers of contraction band necrosis than rats with permanent coronary artery occlusion. Thus, even in the absence of myocardial salvage, late reperfusion significantly limits infarct expansion and remodeling.[37][38] The mechanism for this benefit is probably related to changes of the extracellular matrix and wound healing after myocardial infarction. The effects of late reperfusion on matrix metalloproteinase (MMP) activity have been reported in a rat model.[39] At 7 days after infarction, late reperfusion significantly attenuated MMP-1 and MMP-2 activity compared with rats with permanent coronary artery ligation.[39] MMP-9 activity was also significantly reduced activity at 1 and 2 postinfarction day.[39] Thus, late reperfusion attenuates the activity of a family of enzymes involved in collagen breakdown.

Myocardial apoptosis persists beyond the acute phase of AMI and is associated with LV remodeling.[40][41] Abbate et al.[40] reported that persistent IRA occlusion was associated with an increased myocardial apoptosis in human late after an AMI. The benefits observed with a patent IRA may in part be due to reduced myocardial apoptosis.[40]

Mechanical Effects Associated with Late Reperfusion

It is possible that engorgement of the coronary vascular tree can have a scaffolding effect on the vulnerable infarcted bed, which increases tissue stiffness, to resist early infarct expansion.[42] Another potential advantage involves to collateral vessels. Late reperfusion can provide a conduit for the development of collateral vessels that may support ischemic and possibly hibernating peri-infarct tissue.[1][10] Late reperfusion is also associated with the appearance of contraction band necrosis rather than coagulation necrosis.[43] Coagulation necrosis is more commonly observed in severe and persistent ischemia. The light microscopic findings characteristically do not involve calcification, include nuclear pyknosis, amorphous mitochondrial densities, and stretching of

the myofibrillar elements.[44] Contraction band necrosis, however, results from severe ischemia followed up by reperfusion The histologic appearance frequently includes calcification and dense eosionophilic banding of the cytoplasm.[45] Importantly, the development of contraction band necrosis is related to the rapid influx of calcium ions during the calcium paradox and is associated with systolic arrest of cells and hypercontracture of the myofibrillar apparatus.[45] Thus, reperfusion with contraction band necrosis would be expected to resist infarct expansion.

Late Reperfusion Reduces Arrhythmia Development

The effects of time-independent reperfusion on arrhythmogenesis have been investigated in a number of experimental and clinical studies. Opitz et al.[46] compared the arrhythmia profiles during the first 48 hours of myocardial infarction in rats. Rats subjected to reperfusion after 45 minutes and 90 minutes had significantly reduced infarct sizes compared with rats with permanent coronary artery occlusion. Reperfusion after 180 minutes, however, had no effect on myocardial salvage, with mean infarct size being identical to the mean permanently occluded infarct size.[46] The prevalence of ventricular tachycardia and ventricular fibrillation and incidence of arrhythmic death, however, were significantly reduced in all reperfused rats compared with permanent occlusion.[46]

High-resolution signal averaging of the QRS complex can be assessed for arrhythmia evaluation. A high prevalence of late ventricular after potentials signifies the presence of areas within the myocardium where electrical conduction is slowed or tortuous and, thus predisposes to the development of reentrant ventricular tachycardia.[47] Hohnloser et al.[48] showed a positive correlation between the presence of late ventricular after potentials and an occluded infarct-related artery. In a similar study, the proportion of patients with late ventricular potentials was significantly reduced in patients with reperfusion compared with the patients with no reperfusion, TIMI I or 0, in the infarct related artery.[49]

Autonomic Function and Late Reperfusion

The relationship between autonomic tone and postinfarction arrhythmogenesis may be another mechanism by which late reperfusion may favorably influence prognosis.[50][51] Suppression of the adrenergic drive in AMI by beta-adrenergic blockade improves survival rates.[52][53] Vagal tone after AMI is reduced, thus further potentiating the arrhythmic effects of excess catecholamines. Enhancing vagal responses after AMI have been proposed as a potential antisympathetic and antiarrhythmic strategy. In patient with a patent IRA baroreflex sensitivity was significantly greater than patients with an occluded IRA.[54] The investigators concluded that restoration of IRA patency results in greater baroreceptor sensitivity and vagal activity.[54]

Clinical Trials of Early Reperfusion

The early megatrials of thrombolytic therapy showed the time-dependent benefit of reperfusion. In the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico(GISSI) I trial,[17] a 51% reduction in the mortality rate was observed in patients with AMI who received streptokinase within 1 hour of the onset of symptoms. This benefit progressively decreased to 26% at 3 hours and 20% between 3 to 6 hours. Similarly, in the Second International Study of Infarct Survival(ISIS-2) trial,[18] a 37% reduction in the mortality rate between 0 to 3 hours, a 24% reduction between 3 to 6 hours, and a 17% reduction beyond 6 hours. The Fibrinolytic Therapy Trialist(FTT) collaborative group in their meta-analysis of 9 large trials of thrombolytic therapy showed that the greatest reduction in the mortality rate was observed in patients within 3 hours of the onset of symptoms.[25] In the GUSTO-1 trial,[26] a similar time-dependent benefit was observed; the mortality rate was 4.3% among patients treated between 0 to 2 hours. 5.5% among patients treated between 2 to 4 hours, and 8.9% in patients treated between 4 to 6 hours. As with thrombolytic therapy, time to treatment is a critical determinant of subsequent outcomes after primary percutaneous transluminal coronary angioplasty(PTCA) for AMI. In the GUSTO-IIb angioplasty substudy the 30-day mortality was 1.0% for patients underwent PTCA within 60 minutes of randomization, 3.7% for those treated between 61 to 75 minutes, 4.0% for those treated between 76 to 90 minutes, and 6.4% for patients treated more than 90 minutes after randomization.[55] Primary PCI was shown to be effective[56][57] and an analysis of 23 randomized trials demonstrated improved rates of reinfarction, stroke, and death compared with thrombolysis therapy.[58] Mechanical reperfusion with addition of adjunctive treatment with coronary stent and platelet glycoprotein II_b/III_a inhibitors has gained acceptance.[59]

Very early thrombolytic therapy can abort an AMI. In the Myocardial Infarction Triage and Intervention (MITI) prehospital trial, 40% of the patients treated within 70 minutes of symptom onset had no measurable infarct on thallium tomographic image taken 30 days after treatment.[60]

Clinical Trials of Late Reperfusion

Experimental data suggested that the infarct process

was completed by 4 to 6 hours after coronary artery occlusion. However clinical studies of thrombolytic therapy have shown mortality benefit beyond 6 hours and up to 12 hours after the onset of symptoms. The ISIS-2[18] trial extended the window of time to treatment and showed a significant beneficial effect on mortality rates from streptokinase and aspirin in patients who received treatment between 5 to 12 hours after the onset of symptoms.[18] The Late Assessment of Thrombolytic Efficacy (LATE) trial used alteplase and showed a significant 25.6% reduction in 35-day mortality rates among patients treated between 6 to 12 hours after the onset of symptoms.[61] Similarly the FTT collaborative group meta-analysis reported a highly significant mortality rate reduction among the 13,000 patients presenting at 7 to 12 hours after onset of symptom.[25] These observations led to the acceptance of a 0- to 12-hour time window for the treatment of AMI.

The beneficial effects of thrombolytic treatment beyond 12 hours on 30-day mortality rates are less convincing. In the ISIS-2[18] trial, the patients who received thrombolytic therapy between 12 to 24 hours derived a 19% reduction in mortality rate. The Estudio Multicentrico Estrepquinasa Republicas de America del sul Collaborative Group(EMERAS)[62] trial, however, revealed no significant mortality rate benefit from streptokinase in patients treated beyond 12 hours. The LATE[61] investigators obtained similar results(Fig. 6).

There have been very few prospective randomized studies of late reperfusion beyond 24-hour time window. These studies have been small and insufficiently powered to evaluate clinical endpoints. The TAMI-6 study randomized 197 patients with ST segment elevation myocardial infarction to therapy with tissue plasminogen activator or placebo and subsequently patients with a persistently occluded IRA at 36 hours were randomized to PTCA or no PTCA.[63] Although patency was established in 81% of patients in the PTCA group, only 60% had a patent IRA at 6 months. Conversely, those with an initially occluded vessel and no attempted PTCA had a relatively high(38%) spontaneous patency rate. At 6 months, no difference was seen between the PTCA and no PTCA groups with respect to mortality, ventricular volumes, and systolic function. However, Horie et al.[64] studied the effect of late reperfusion by PTCA in 83 patients with anterior myocardial infarction more than 24 hours after the onset of symptoms. Patients assigned to the PTCA treatment group had significantly less LV dilatation at 6 months. Long-term follow-up over 50 months revealed a statistically significant decrease in the combined endpoint of death, recurrent AMI, and congestive heart failure. Yousef et al.[65] randomized 66 symptom-free patients with single vessel disease, left anterior descending artery occlusion, to delayed intervention with stent or medical treatment 26 days after transmural anterior myocardial infarction. They demonstrated a significant increased left ventricular endsystolic volume in the late reperfusion group compared to patients receiving optimal medical treatment at 12 month. In the case of symptomatic chronic total occlusion of IRA after transmural infarction or in patients with significant residual myocardial viability, significant benefits from late intervention could be possible.[66] Thus, data on very late reperfusion have remained inconclusive. Recently, the Occluded Artery Trial[13] answered the question of the very late effects of reperfusion on clinical outcome in stable patients with AMI.

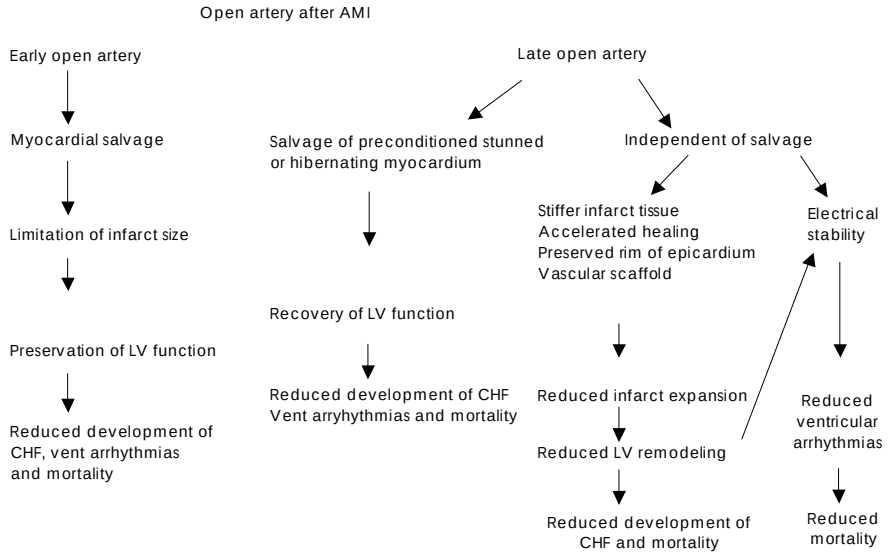

Fig. 6. Mechanisms of benefit. Early versus late open artery after acute myocardial infarction.[3] AMI: acute myocardial infarction, CHF: congestive heart failure, LV: left ventricle.

The Occluded Artery Trial

Hochman et al.[13] published an article about the late reperfusion of the IRA after AMI. This trial answered questions about the late open-artery hypothesis in the clinical field. These investigators randomized 2,166 stable patients who had total occlusion of the IRA 3 to 28 days after AMI and who had a high-risk criterion such as an ejection fraction of less than 50% or proximal occlusion. Of these patients, 1,082 patients were assigned to routine PCI and stenting with optimal medical therapy, and 1,084 patients were assigned to optimal medical therapy alone. The primary end point was a composite of death, myocardial reinfarction, or New York Heart Association(NYHA) class IV heart failure. The results were as follow. The 4-year cumulative event rates were 17.2% in the PCI group and 15.6% in the medical therapy group(hazard ratio 1.16, p=0.20). Rates of fatal and nonfatal myocardial infarction were 7.0% and 5.3% in the two groups respectively(hazard ratio 1.36, p=0.13). Rates of nonfatal myocardial infarction were 6.9% and 5.0%, respectively(hazard ratio 1.44, p=0.08). Rates of NYHA class IV heart failure(4.4% vs. 4.5%) and death(9.1% vs. 9.4%) were similar. This study showed high rates of procedural success with PCI and sustained patency but showed no clinical benefit during an average 3-year follow-up with respect to death, reinfarction, or heart failure, contrary to the hypothesis. Moreover, a trend toward an excess risk of reinfarction in the PCI group aroused concern. As the ancillary study of the OAT, the Total Occlusion Study of Cancda (TOSCA)-2 trial[67] was conducted to determine whether opening a persistently occluded IRA by PCI in patients beyond the acute phase of myocardial infarction improved patency and indices of left ventricular size and function. In the TOSCA-2 trial, 381 patients with an occluded IRA 3 to 28 days after AMI(median 10 days) were randomized to PCI with stenting or optimal medical therapy alone. Repeat coronary and LV angiography were performed 1 year after randomization. At 1 year, 83% of PCI group versus 25% of medical therapy group had a patent IRA (p<0.001). The LV ejection fraction increased significantly in both groups, with no between group difference. The median change in the LV end-systolic volume index and the LV end-diastolic volume index were not significantly different. This study concluded that a strategy of PCI to recanalize occluded IRAs in stable patients 3 to 28 days after AMI was effective in maintaining the long-term patency of the IRA but did not improve the LV ejection fraction. Progressive LV dilatation over 1 year appeared to be modestly attenuated in the subset with available data. On the basis of these results, routine PCI is not recommended for persistent IRA occlusion in stable patients in the days to weeks after AMI. Patients without spontaneous or inducible myocardial ischemia in whom LV systolic function is not depressed, routine coronary angiography, often performed previously to identify a persistently occluded IRA, is not recommended.[68]

Conclusion

Reperfusion therapy in patients with AMI is one of the major medical advances of the late 20th century. In the thrombolytic era, the benefit was greatest when such therapy was initiated within 1 hour of symptom onset. Early reperfusion of the IRA within 3-6 hour can salvage ischemic myocardium and preserve ventricular function and improve patient survival. The original "open artery theory" notion is based on a "time-dependent" effect. The concept that a patent IRA and myocardial reperfusion confer benefit beyond that resulting from myocardial salvage has given rise to the "open-artery hypothesis". A variety of indirect evidence suggests the benefit of late reperfusion of IRA in AMI patients. The mechanisms of reperfusion therapy except reduction of infarct size include the limitation of infarct expansion, the reduction of LV remodeling development, the scaffolding effect of reperfused vessels, a conduit for collateral vessel, the improvement of the blood supply to hibernating myocardium, increased infarct wound healing, development of contraction band necrosis rather than coagulation necrosis in infarct myocardium, reduction of myocardial apoptosis, increased baroreceptor sensitivity and vagal activity, and reduced ventricular arrhythmia. These mechanisms extended the time window of ischemia to 12 hours and possibly 24 hours after the onset of AMI. On the basis of the OAT study, however, routine PCI 3 days to weeks after AMI is not recommended for persistently occluded IRA in asymptomatic high risk patients.

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