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The Open-Artery Hypothesis: An Overview

Carey D. Kimmelstiel and Deeb N. Salem

Tufts University School of Medicine; Adult Cardiac Catheterization, Laboratory and Ambulatory Cardiology, New England Medical Center Boston, Massachusetts, USA

Abstract. **The open artery hypothesis postulates salutary effects distinct from myocardial salvage referable to infarct related arterial patency. Short and long term clinical trials, as well as studies in animal models have suggested clinical benefit in patients with sustained infarct related arterial patency. Mechanisms of benefit are not entirely clear, but probably relate to mitigation of post infarction left ventricular remodeling and improvement in several electrophysiologic parameters. The effect of infarct related arterial patency on post infarction prognosis, presumed mechanisms of benefit and noninvasive assessment of arterial patency are summarized in this review.**

Key Words. **infarct related artery, patency, remodeling**

In 1980 DeWood and colleagues firmly established thrombotic coronary occlusion as the inciting event in myocardial infarction (MI) [1]. Subsequent large clinical trials have documented the efficacy of thrombolytic therapy and have revolutionized the treatment of MI. Prior work in animal models documented a finite time period in which relief of epicardial coronary occlusion would prevent myocardial necrosis [2], while early thrombolytic mega trials showed disproportionate benefit with early treatment [3,4]. Consequently, the predominant mechanism initially proposed to explain the efficacy of thrombolytic therapy was preservation of left ventricular (LV) contractility via re-establishment of coronary patency.

Large thrombolytic trials and meta-analyses of these studies have revealed only marginal improvement in global left ventricular systolic function [5,6], an effect usually fully apparent by 4 days following treatment [7]. Thus, the survival benefit attendant to thrombolytic therapy seems to greatly exceed that which can be explained by improved left ventricular function [6,8]. Indeed, striking reductions in mortality with no beneficial effects on global or regional left ventricular function have been noted in response to intracoronary and intravenous thrombolysis [9,10]. Furthermore, survival benefit has been demonstrated in MI patients anywhere from 6 to 24 hours after the onset of symptoms in patients treated with thrombolysis [4,11,12], a time generally perceived as being too late to affect myocardial salvage. Of importance, several studies have revealed that patency of the infarct-related artery had negligible effects on left ventricular function yet was an independent prognostic factor in determining survival [13,14]. One meta-analysis of 33 thrombolytic trials documented reduced mortality even when thrombolysis was instituted 12–24 hours after symptom onset [12], a time when significant myocardial salvage is unlikely. Other reviews of existing data have documented a survival benefit associated with thrombolytic therapy that cannot be explained by the small effect on left ventricular ejection fraction [15–18]. As well, other authors have noted fairly profound reductions in 1-year mortality in patients with left ventricular dysfunction treated with thrombolytic therapy followed by high rates of revascularization when compared with similar patients from the prethrombolytic era [16].

These observations have led to the development of the "open-artery hypothesis," which postulates time-independent advantages to infarct artery patency that are distinct from the time-dependent benefit of myocardial salvage. This brief summary reviews the beneficial effects of infarct-related artery patency on post-MI prognosis and focuses on the suggested mechanisms for this benefit.

Patent Infarct-Related Artery: Effects on Prognosis

Effects on short-term mortality

Evidence supporting a beneficial effect of infarct-related artery patency on mortality date back to early thrombolytic trials. In the Western Washington Intracoronary Streptokinase Trial, at 1-month follow-up, patients with a patent infarct-related artery (IRA) had half the mortality of those with a closed artery. The difference in mortality between the two groups became more apparent at 1-year follow-up, with patients with patent IRAs having less than one-fifth the mortality of those with occluded arteries [19]. Similar results were seen in the TIMI-1 trial, with impressive reductions in 21-day and 1-year mortality in patients with patent IRAs [20–22].

The beneficial effect of a patent IRA on short-term mortality suggested by early thrombolytic trials was extended by German investigators reviewing data

Address for correspondence: Carey D. Kimmelstiel, MD, New England Medical Center, Box 264, 750 Washington Street, Boston, MA 02111. email: carey.kimmelstiel@es.nemc.org

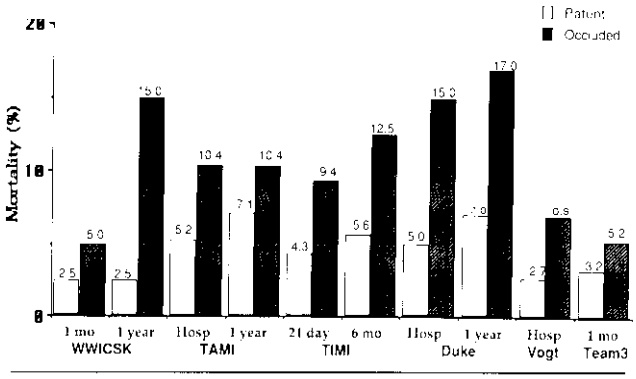

Fig. 1. The effect of infarct-related artery patency on survival in various thrombolytic trials. (Adapted from references 19–24.)

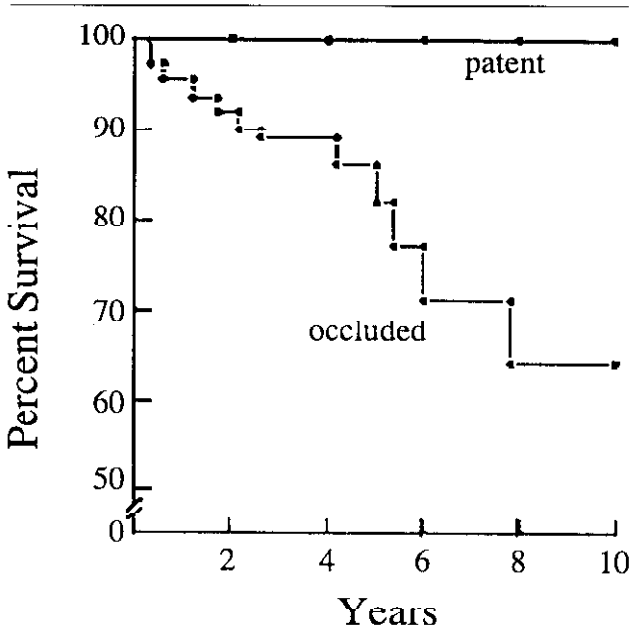

Fig. 2. Long-term survival in patients with single-vessel coronary disease. $p < 0.003$ between patent and occluded groups. (From Cigarroa et al. [36], with permission.)

from four multicenter thrombolytic trials. They documented that early, complete reperfusion of the IRA as determined by coronary angiography 90 minutes after the initiation of thrombolytic therapy was associated with the significant reduction in early mortality [23]. These authors noted that only TIMI grade III flow conferred a survival benefit; patients with TIMI grade II flow fared no better than those with TIMI 0/1 flow [23]. This important observation has subsequently been confirmed by investigators from the Team 3, GUSTO, and European Cooperative Study Group Thrombolytic trials (Fig. 1) [24–26].

The beneficial effects of IRA patency following thrombolytic therapy for acute MI has been extended by investigators reporting results from trials studying primary and rescue coronary angioplasty (PTCA) strategies. Primary PTCA studies have shown significantly more frequent IRA patency in patients treated with PTCA as compared with thrombolytic therapy associated with reduced occurrence of death and re-infarction [27,28]. Most interestingly, these trials have not, in general, documented enhanced myocardial salvage [27,29]. PTCA leading to patency of the infarct-related artery has also been shown to have beneficial effects on survival when compared with less invasive strategies in patients failing to respond to thrombolytic therapy [30–32], patients manifesting cardiogenic shock [33,34], and other high-risk subsets [35]. The similarities of patient populations in terms of demographic variables and degree of coronary artery disease and the lack of consistent improvement in indices of left ventricular performance following improved rates of patency in patients treated with PTCA provides putative evidence for an independent salutary effect of IRA patency and prognosis following MI.

Effects on long-term mortality

Independent salutary effects on long-term prognosis referrable to patency of the IRA is suggested by several sources. Cigarroa and colleagues retrospectively analyzed patients with single-vessel coronary artery disease who underwent cardiac catheterization following an MI. They compared patients with partial or complete anterograde flow to those with minimal or no flow through the IRA and found that survival correlated most significantly with a patent IRA (Fig. 2) [36]. Over an approximately 5-year follow-up no patients with a patent IRA died, while 18% of those with minimal IRA perfusion expired ($p < .001$, see Fig. 2) [36]. In addition, those with minimal perfusion of the infarct-related artery more frequently developed heart failure, unstable angina, and MI [36].

A similar analysis was performed by McCully et al., who examined medically treated patients with isolated left anterior descending (LAD) disease from a large registry of patients with cardiac disease [37]. In patients with a prior anterior MI, they documented significantly improved survival with a patent LAD over a 5-year follow-up period. Patency of the LAD was not an independent predictor of long-term survival when subjected to multivariate analysis [37]; however, a significant long-term survival advantage was seen in younger patients (age <70 years) with a patent vessel versus those with an occluded artery who had no collateral blood supply to the infarcted region [37]. The survival benefit in these patients was most marked when LV dysfunction was present [37]. It should be noted that these investigators employed a somewhat arbitrary definition of patency related only to the visual estimation of stenosis severity that did not consider flow in the IRA.

Shröder et al. reported on patients from the ISAM trial in whom reperfusion was achieved late and were

subsequently followed for approximately 3 years [38]. Angiographic study of coronary anatomy was performed an average of 1 month following MI. Using a strict definition of patency incorporating both TIMI grade flow and stenosis severity in the IRA, and limiting their analysis to patients with anterior MIs, mortality on long-term follow-up in patients with a patent versus occluded LAD was 8% and 28%, respectively ($p < .03$) [38].

Galvani and associates performed a retrospective analysis on a relatively stable cohort of patients with single-vessel coronary artery disease surviving a first Q-wave MI who underwent coronary angiography prior to hospital discharge. They examined long-term prognosis of TIMI 0–1 vs. II–III grade flow in the IRA [39]. Ten-year follow-up documented a low overall mortality rate of 9%; however, 15 of the 16 documented deaths occurred in patients with TIMI 0–1 flow ($p < .001$ between the two groups) [39]. In patients with left ventricular dysfunction defined by an elevated end-systolic volume index, the mortality was 2% in those with TIMI II–III flow versus 30% in patients with TIMI 0–1 flow ($p < .001$) [39]. Multiple logistic regression analysis found survival to be most significantly related to end-systolic volume index and IRA patency [39].

The potential importance of IRA patency in patients with LV dysfunction was underlined in the study by White et al. They reported on the long-term follow-up of over 300 patients treated with thrombolytic therapy who had coronary angiography performed approximately 1 month following MI. Employing an occlusion score that considered both TIMI grade flow and the amount of myocardium supplied by the IRA using multivariate analysis, they documented that for patients with a left ventricular ejection fraction (LVEF) less than 50%, an occluded IRA (defined as less than TIMI III grade flow) was associated with an adverse prognosis regardless of its myocardial distribution [14]. When LVEF was equal to 50%, an occluded vessel portended a poor prognosis when it supplied approximately 25% of the LV [14]. These investigators highlighted the independent long-term prognostic importance of arterial patency in addition to LV function following thrombolytic therapy.

Valuable data regarding the prognostic importance of IRA patency comes from recently published results of the SAVE trial. Performing long-term follow-up (average 3.5 years) in post-MI patients with LV dysfunction, these investigators documented that an occluded IRA was an independent predictor of all-cause (patent vs. occluded 14% vs. 24%) and cardiovascular mortality (12% vs. 23%) as well as the composite endpoint of cardiovascular mortality or morbidity (37 vs. 51%, $p < .001$ for all comparisons; Fig. 3) [40]. The salutary effects of IRA patency were noted independent of the benefits attendant to medical therapy, such as angiotensin-converting enzyme inhibition and beta-blockade [40]. This study differed from other studies in that IRA patency was a prespecified ancillary endpoint of the SAVE study, the analysis was restricted to post-MI patients with LV dysfunction without clinically apparent ischemia or heart failure, baseline coronary anatomy was known in all patients, a variety of treatment strategies culminating in IRA patency were included, and corrections for clinical variables including LV function were made. Most recently, IRA patency following PTCA performed for post-MI ischemia has been shown to result in enhanced long-term survival, especially in patients with LV dysfunction [41].

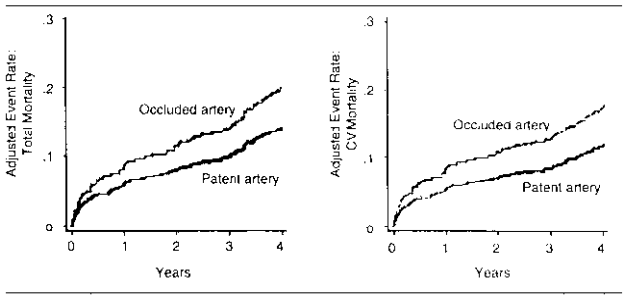

Fig. 3. *Adjusted total ($p = 0.044$, occluded vs. patent) and cardiovascular mortality ($p = 0.029$) in patients with occluded and patent infarct-related arteries in the SAVE trial. CV = cardiovascular. (Adapted from Lamas et al. [40], with permission.)*

Table 1. *Proposed mechanisms to explain the open-artery hypothesis*

Effects on post-MI LV remodeling
Effects on infarct healing
Electrophysiologic effects
Perfusion of hibernating myocardium
Collateral blood supply to distant ischemic myocardium

LV = left ventricular; MI = myocardial infarction.

IRA Patency: Potential Mechanisms of Benefit

Effects on left ventricular remodeling and infarct healing

Several mechanisms have been postulated to explain post-MI benefits conferred by patency of the IRA (Table 1). These various mechanisms are described here. The salutary effects conferred by patency of the IRA may relate to mitigation of postinfarction LV remodeling. The remodeling process consists of infarct expansion and subsequent LV dilatation [42], a process that is most common in large transmural MIs. Expansion involves thinning and lengthening of damaged muscle soon after infarction, with later dilation and hypertrophy of noninfarcted segments continuing, even after completion of infarct expansion [17,42,43], which may be associated with distortion in LV shape, such as

aneurysm formation [42]. The remodeling process frequently causes augmentation in LV volume, which has been found to be a powerful correlate of diminished post-MI prognosis [44]. Investigations in animals and patients have documented that the degree of LV dilation is directly proportional to the initial extent of myocardial necrosis and is not secondary to elevation in ventricular filling pressures [42,45–51]. In general, the remodeling process occurs when infarction involves more than 20% of the of LV circumference [42,45].

Studies performed in a variety of animal species have documented that coronary reperfusion too late to effect myocardial salvage can have marked effects on prevention of left ventricular remodeling. In rats with early, delayed, and permanent coronary ligation, Hochman and Choo documented decreased infarct expansion in rats with late reperfusion compared with permanently ligated animals, with no differences in infarct size or degree of infarct transmurality [52].

Late reperfusion in dogs was associated with reduced diastolic and systolic infarct expansion [53], with similar results noted by other investigators [54]. Hale and Kloner in a rat model showed that although late reperfusion did not decrease infarct size, it did diminish both left ventricular expansion and wall thinning [55]. In a carefully performed rat study, Boyle and coworkers documented significantly diminished infarct expansion and remodeling, with no effect on infarct size with late reperfusion [43]. These investigators established that late reperfusion led to a permanent reduction in postinfarction remodeling and suggested that this effect is not as time dependent as is the influence of early reperfusion on infarct size [43]. Recently, Mallavarapu et al. compared rats with permanently ligated left coronary arteries to a group undergoing late reperfusion, documenting not only decreased left ventricular volumes but diminished mortality in the reperfused group [56].

Retrospective reviews of patients treated for MI have in large measure borne out the results of the above-mentioned animal studies. Jeremy et al. examined the relation between IRA perfusion on left ventricular volume and function in the month following MI in patients not receiving thrombolytic therapy or PTCA. Defining patency as TIMI grade II–III flow, these investigators reported left ventricular dilation in 100% of patients with an occluded vessel, but in only 8% of those with patent arteries, with no differences in infarct size noted between the two groups [57]. Multivariate analysis identified degree of perfusion of the infarct-related artery as the variable most closely correlated with change in left ventricular volume [57]. Similarly, retrospective multivariate analysis of patients in four TAMI studies documented better regional function and more profound improvement in global ejection fraction at 1 week in patients with patent infarct-related arteries [58]. These findings have been extended by Leung and Lau, who studied a series of patients with single-vessel coronary artery disease and an initial MI treated with thrombolytic therapy. They documented that the degree of residual stenosis in the IRA was an important predictor of subsequent LV dilation on long-term follow-up, and patients with total occlusion of the IRA demonstrated the greatest degree of remodeling and functional impairment [59].

A primary PTCA trial examining approximately 400 patients revealed similar ejection fractions in patients with occluded and patent IRAs. However, on long-term follow-up, ejection fraction improved in patients with patent vessels while worsening in patients whose IRA was occluded [60].

Several groups have used echocardiographic techniques to examine the effect of patency status of the IRA on left ventricular remodeling. Siu et al. examined patients treated with thrombolytic therapy for first MI, comparing endocardial surface area index (ESAi) and percentage abnormal wall motion (AWM) in patients with and without IRA patency. Although limited by a high rate of patient exclusion and a limited definition of patency, they noted on long-term follow-up an increase in ESAi in patients with occluded arteries compared with patients whose IRA was patent [61]. They also reported a significant decrease in AWM in the group of patients with patent IRAs, while there was no change in the occluded group [61]. With a strict definition of patency, studying MI patients with single-vessel disease treated with thrombolytic therapy, Agati et al. used contrast echocardiography to measure regional and global left ventricular function in a cohort of patients with patent IRAs. After 6 months of follow-up they documented improvement in both regional and global function in patients with a patent IRA if residual perfusion in the infarct zone existed [62].

Povic et al. performed sequential echocardiographic analyses of 31 consecutive patients presenting with an initial MI, examining the complementary effects of thrombolysis and arterial patency on LV function and size. In a very well-done study, these investigators showed that thrombolytic therapy was the predominant determinant of initial ventricular volume and function, while late vessel patency was the predominant determinant of future ventricular dilation [63]. Their results strongly suggested that thrombolytic therapy and late IRA patency have independent and complementary roles in preserving ventricular size and function.

Data from several trials primarily examining reperfusion performed late in the setting of MI support the concept of patency of the IRA conferring a salutary effect on LV remodeling. Retrospective review of data from the ISAM trial showed late revascularization led to improved global and regional LV function 1 month following MI [38]. Examination of a small

cohort of late thrombolized patients documented mitigation of LV dilation in patients with successful reperfusion [64]. In a double-blind, placebo-controlled study, Topol and coworkers demonstrated prevention of LV dilation 6 months after MI in patients randomized to late thrombolysis [65]. Nidorf et al. in a prospective study of the natural history of MI used echocardiographic techniques to study the relation between timing and adequacy of perfusion of the infarct bed to changes in regional function and LV size. Their data showed progressive reduction in extent of abnormal wall motion in patients with both early and late restoration of antegrade flow to the IRA [66]. On long-term follow-up, multivariate analysis showed that patency of the IRA was the only significant predictor of change in abnormal wall motion in the infarcted territory [66]. Hirayama and coworkers examined 89 patients with an initial anterior MI, studying the relation between infarct size and ultimate LV cavity size, clarifying the benefit of late reperfusion. These investigators performed a rigorously controlled analysis documenting no change in infarct size by late reperfusion; however, they did note that patients with early, intermediate, and late reperfusion had significantly lower end-diastolic and end-systolic volume indices when compared with nonreperfused patients [67]. As LV volumes significantly increased only in nonreperfused patients, they concluded that late reperfusion prevents postinfarction ventricular dilation independent of limitation of infarct size [67].

Studies examining late mechanical revascularization of the IRA as well as those that have looked at patients who suffer late IRA reocclusion without reinfarction have also suggested a salutary effect of IRA patency on LV remodeling. The APRICOT trial reported on patients with angiographic reocclusion without reinfarction 3 months following initially confirmed IRA patency shortly following thrombolytic therapy. This trial noted improved LVEF in the group not experiencing IRA reocclusion. Multivariate analysis highlighted that IRA patency accounted for LVEF differences between patients with and without reocclusion [68]. Confirmed long-term IRA patency was associated with improved infarct zone regional wall motion and a decrease in end-systolic volume index when elevated at baseline [68]. This study strongly suggested that IRA reocclusion without reinfarction is detrimental to regional and global LV function following MI. Miketic et al. examined late (2–8 weeks following MI) IRA PTCA's effect on late LV function in patients with high-grade residual stenosis, compromised blood flow, and documented ischemia following initial MI. Six months after successful reperfusion (achieved in 85% of patients), there was an improvement in global LVEF (57–62%, $p < 0.001$) [69]. This improvement, not noted in patients without successful reperfusion, was attributed to improved infarct-zone regional wall motion [69]. Mitigation of left ventricular remodeling following mechanical revascularization of the IRA is supported by data from the SAVE study. Patients whose IRA was initially occluded, then opened (the vast majority of whom underwent PTCA), subsequently had a small but significant improvement in LVEF compared with patients whose IRA was persistently occluded (32 ± 6% vs. 30 ± 7%, $p = 0.023$) [40]. The apparent small improvement in global LV function associated with re-establishment of IRA patency was associated with marked reductions in total mortality (occluded, then opened vs. persistent occlusion: 11 vs. 24%, $p = 0.004$), cardiovascular mortality (9 vs. 23%, $p = 0.001$), and the trial's composite endpoint (32 vs. 51%, $p = 0.002$) [40]. Pfeffer et al., examining the effect of captopril on ventricular dilation after MI, noted that persistent occlusion of the IRA was the most important baseline variable predicting subsequent left ventricular enlargement [70].

Several mechanisms have been postulated to be responsible for mitigation of post-MI remodeling in the absence of myocardial salvage by re-establishment of IRA patency. It has been suggested that perfused coronary vasculature in a region of necrosis could provide a functional "scaffolding," providing structural support, and thus limiting subsequent expansion and dilation [6,16,71]. Late reperfusion-induced regional myocardial stiffening or reduction in compliance has been documented in dog models following relief of coronary occlusion [54,72]. Some have suggested that this reduction in regional compliance is due to myocardial hemorrhage [73,74] or edema [75]; however, these changes are controversial and not universally noted [54].

Salvage of a rim of myocardial tissue has been proposed by some as a mechanism whereby late reperfusion prevents infarct expansion [42,76]; however, histologic study in animal models has not supported this hypothesis [43,52]. Beneficial effects of late reperfusion may relate to a change of the type of myocardial necrosis from coagulation to contraction band [43,54,74]. Boyle and colleagues reported significantly greater myocytolysis associated with contraction-band necrosis in rats subjected to late reperfusion [43]. Histologically this was associated with cellular remnants or sarcolemmal shells, not seen in permanently ligated animals with coagulation necrosis [43]. These cellular shells were postulated to serve as a scaffold, buttressing the infarcted region, acting to mitigate future remodeling [43].

A variety of investigators using differing techniques in diverse animal models have noted an accelerated rate of infarct healing in response to late reperfusion [43,52,73,77]. Some have suggested this is due to a washout of chemotactic factors, leading to tissue degeneration or to an increase in the influx of proteins, such as fibronectin, which act to repair injured myocardial tissue [73,74]. Thus, although there is lit-

Table 2. *Electrophysiologic effects associated with post-MI IRA patency*

Reduced succeptibility to and inducibility of ventricular arrhythmias
Reduced incidence of late potentials
Mitigation of postinfarction autonomic dysfunction

MI = myocardial infarction; IRA = infarct-related artery

tle doubt that IRA patency is an important modifier of peri-MI remodeling, the definitive protective mechanism(s) remain unclear.

Effects on electrophysiologic parameters

There exist data that suggest an electrophysiologic basis for IRA patency (Table 2). In 1986, Kersschot et al. demonstrated that sustained ventricular arrhythmias were less commonly induced in patients with early post-MI reperfusion following thrombolytic agents [78]. In 1989, Théroux et al. found that PVCs on 24-hour monitoring were significantly less common in post-MI patients who had received streptokinase or PTCA [79]. Subsequently, several investigators reported that patients treated with thrombolysis were less likely to have inducible ventricular arrhythmias post-MI than those treated conservatively [80–82]. The TIMI phase II trial reported on 2546 patients without congestive heart failure or hypotension during the first 24 hours following acute MI; 1.9% of these patients developed sustained ventricular tachycardia or ventricular fibrillation [83]. IRA patency was seen in only 68% of the ventricular tachycardia or ventricular fibrillation patients, while patency was present in 87% of patients without life-threatening arrhythmia ($p = 0.01$) [83]. Hii et al. studied 64 patients who had sustained an MI and presented with ventricular tachycardia or fibrillation. These investigators performed electrophysiologic studies and found that a patent IRA predicted a more successful response to drug therapy (45% vs. 9%, $p = .001$) and that a patent IRA was the only independent predictor of such a response [84].

In the late 1980s the relationship between signal-averaged electrocardiographic (SAECG) abnormalities and thrombolytic therapy, PTCA, and IRA patency began to be reported. Gang et al. found only a 5% incidence of late potentials in patients treated with thrombolytic therapy compared with a 23% incidence in those untreated ($p = 0.01$) [85]. Furthermore, no patients in the treatment group with patent vessels had evidence of late potentials [85]. De Chillou and coworkers found that a patent IRA was the most important factor predicting the absence of late potentials following an initial MI [86]. These findings were challenged by various groups who found no significant differences in signal averaging between treated and untreated patients [87–90].

These conflicting results of studies of SAECG abnormalities following thrombolytic therapy were somewhat clarified in a report by Chew et al. [91]. They examined a cohort of post-MI patients treated with thrombolytic therapy using 25-Hertz and 40-Hertz SAECG filtering. The significant differences in the SAECG incidence of late potentials were only found in the 40-Hertz group, suggesting that the conflicting results may be explained by differences of band-pass filtering frequency.

Several investigators have looked at the relationship between patent IRAs and late potentials. Aguirre found that the mean number of premature ventricular contractions and late potentials was higher in patients with occluded arteries versus open arteries (54% vs. 19%, $p < 0.03$) [92]. In this study, PVC frequency and late potentials were not influenced by the time to thrombolytic therapy, that is, less than 2 hours versus 2–6 hours [92]. Steinberg et al. reported on SAECG abnormalities for the LATE trial, which studied patients treated with r-tPA 6–24 hours post-MI versus placebo. The abnormal finding of a filtered QRS duration greater than 120 msec was seen 37% less frequently in r-tPA–treated patients than in the placebo group, and in all cases benefit was seen in patients with ST-segment elevation [93]. Boehrer et al. examined a small group of patients who underwent PTCA 6–15 days post-MI and compared them to patients who were treated conservatively. In a 3- to 7-month follow-up period, the PTCA group had a significant decrease in SAECG abnormalities, while the untreated group had no improvement [94]. However, in a similar study, Ragosta et al. concluded that late perfusion had little effect on SAECG abnormalities [95].

Hohnloser et al. studied 173 acute myocardial infarction patients, 51% of whom had been treated with thrombolysis. One hundred and thirty-six had a patent IRA, and 24% of these exhibited late potentials [96]. Regional ischemia in this cohort was treated with coronary artery bypass surgery or PTCA. In a 1-year follow-up using multivariate analysis, these authors concluded that an open IRA and regional wall-motion abnormalities were the strongest predictors of late potentials, and only an occluded IRA was a predictor of arrhythmic complications [96].

There has been a growing body of evidence suggesting a relationship of SAECG abnormalities to post-MI ventricular dilitation and remodeling. Zamen et al. found that the presence of late potentials the first week following MI correlated with an increase in the end-diastolic volume index (EDVI) as compared with a decrease in EDVI in late potential negative patients [97]. The Consensus II trial evaluated the use of intravenous enalaprilat in the first 24 hours of acute MI followed by oral enalapril and found that the presence of late potentials was associated with a lack of improvement in left ventricular function [98]. The presence of late potentials improved in the enalapril-treated group, both at discharge and at 3–6 months

[98]. Recently, in a thought-provoking study, Chamiec reported preliminary evidence that the use of antioxidants (vitamins C and E) post-MI, reduced oxygen free radical production as measured by isolated leukocytes and that the vitamin-treated group had no significant changes in SAECG, while the untreated group had significant increases in SAECG abnormalities [99].

Over the past several years, the finding of a decrease in autonomic tone following myocardial infarction has been actively investigated. Odemuyiwa et al. examined the relationship between infarct artery patency, left ventricular function, and heart rate variability (HRV) in 186 acute MI survivors. They found that HRV was significantly depressed in patients with systolic ejection fractions less than 40% and an occluded IRA compared with patients with a patent IRA (22 % vs. 8%) [100]. Copi et al. examined 579 post-AMI patients over a 2-year period, looking at predischarge heart rate, ejection fractions, and HRV. They found that an increase in predischarge heart rate was as strong a predictor of sudden death as HRV and systolic ejection fraction [101]. Kontopoulos et al. studied 60 patients status post-MI, who were randomized to quinapril, metoprolol, or placebo and measured HRV 35 days postinfarction. These investigators found that both quinipril and metoprolol significantly increased HRV, suggesting benefit from both these agents [102]. Mortara reported on 359 patients in the Autonomic Tone and Reflexes after MI (ATRMI) study, examining baroreflex sensitivity (BRS) following treatment with phenylephrine. Patency of the IRA was associated with a higher BRS values (8.9 $\pm$ 5.8 vs. 7.1 $\pm$ 4.7 msec/mmHg $p < .005$) and was associated with a lower incidence of a markedly depressed BRS (9% vs. 18%, $p < 0.02$), which is considered to be related to post-MI mortality [103].

A number of studies have followed patients treated for myocardial infarction with thrombolysis or PTCA looking for evidence of a decrease in ventricular tachycardia, ventricular fibrillation, or sudden death. The results of these studies are mixed. Studies by various investigators found significant decreases in these electrophysiologic complications following thrombolytic treatment and/or IRA patency [36,81,96]. However, other studies have failed to show any significant benefit [80,104].

In summary, currently available evidence suggests that the frequency of late potentials is reduced by thrombolytic therapy, particularly in the presence of a patent IRA and that IRA patency may also improve post-MI autonomic dysfunction. There also appears to be a relationship between electrophysiologic parameters, such as late potentials, to post-MI heart size. Of greater importance is the finding that high-risk post-MI patients may be less likely to have sustained ventricular arrhythmias induced by programmed stimulation if their IRA is patent and that post-MI patients with patent IRAs have preserved autonomic function and may be at a lower risk of life-threatening arrhythmias.

Other potential mechanisms

PTCA of highly stenotic vessels days to weeks following MI has been shown to result in improved regional wall motion in the infarcted distribution [105]. Similarly, late PTCA of a vessel supplying myocardium supported by collateral blood supply has been documented to result in improved ventricular function [106]. These observations suggest that perfusion of hibernating myocardium is another mechanism whereby patency of the IRA can confer beneficial effects following MI. Others have suggested that by providing collateral supply to distant ischemic territories, open IRAs provide protection to remote segments of myocardium [8].

Noninvasive Assessment of Arterial Patency

Important prognostic information could be obtained if a noninvasive modality for determining IRA patency were available. There has been suggested utility of ST-segment recovery analysis [107–109] and vectorcardiographic monitoring [110]. These techniques appear limited due to marginal sensitivity, a need for ancillary equipment, and the fact that predictions of patency are valid only in the peri-infarction period. Measurement of total plasma creatine kinase (CPK) activity [111], CPK MM isoforms [112], and plasma fibrinopeptide A levels [113] have been reported to predict IRA patency; however, there is a significant overlap between patient groups [112], low sensitivity [113], and utility only in the immediate peri-infarction period. Clinical variables such as repeated blood pressure measurement [114] and combinations of various noninvasive parameters [115,116], including scintigraphic, echocardiographic, and magnetic resonance imaging [117–119], are also limited due to an inability to predict IRA reocclusion after the peri-infarction period and lack of the validation in clinical trials.

Conclusions

The preceding discussion details relevant data concerning the benefits associated with IRA patency following MI. Although there are published data that do not support the open-artery hypothesis [120,121], the majority of published data concerning this theory do support the concept that clinical benefit is derived from post-MI vessel patency. The precise mechanisms responsible for this benefit are not clear, but attenuated left ventricular remodeling and electrophysiologic benefits are probably the most important factors.

Despite the accumulating data suggesting salutary effects of prolonged vessel patency following MI, one cannot conclude that patients surviving MI should be

routinely intervened upon. What is necessary is a clinical trial in which this hypothesis can be tested in a randomized fashion. The preceding discussion strongly suggests that a patent IRA exerts salutary effects on post-MI remodeling independent of an effect on myocardial salvage. Examination of data from some studies suggest that those patients with occluded IRAs may start out with larger (albeit not statistically significantly larger) left ventricles [42,59]. A large trial that examined the hypothesis of reestablishing IRA patency in patients with, for example, initial anterior MIs would be able to conclusively define whether or not the trend toward larger hearts in patients with occluded IRAs initially noted in some clinical studies plays an important role in subsequent remodeling. In addition, what would be clinically important would be a noninvasive exam to predict not only peri-infarct vessel patency, but also one that could suggest reocclusion at a later time.

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