The Open-Artery Hypothesis: An Overview

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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 0 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 review summarizes 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-4 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

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227
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 referable to patency of the IRA is suggested by several sources. Cigarroa and colleagues retrospectively analyzed patients with single-vessel coronary artery disease who underwent coronary catheterization following an MI. They compared patients with partial or complete antegrade 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 period, those 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.

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