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**REVIEW ARTICLE****Reperfusion Strategies for Acute Myocardial Infarction: Mechanical vs. Thrombolytic Therapy**

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**Introduction**

Management of patients with acute myocardial infarction represents a great challenge to emergency physicians, a task more recently complicated by the myriad of potential treatment options available. The goal of reperfusion therapy in patients with ST segment elevation myocardial infarction (STEMI) is the safest, earliest and most complete restoration of normal (TIMI-3) flow in the infarct related artery. Current strategies include thrombolysis, primary angioplasty or a combination of the two. Recent advances in antiplatelet and antithrombotic therapy with glycoprotein IIB / IIIA inhibitors and low molecular weight heparins have introduced another option, multimodal combination pharmacological therapy.<sup>1,2</sup>

Multiple clinical trials which included thousands of patients undergoing thrombolytic therapy for STEMI have demonstrated a substantial improvement in mortality with their use.<sup>3</sup> The principle determinants of survival after reperfusion therapy are speed of reperfusion and the magnitude of patency restoration. Retrospective analysis by Tiefenbrunn and Boersma of data from more than 20 clinical trials demonstrates a clear time dependant benefit from reperfusion therapy.<sup>4,5</sup> In both models, the benefit / time curve is very steep until approx 2 hours after symptom onset, suggesting the greatest benefit was achieved early, with more modest results occurring between 2 and 12 hours after symptom onset. Therapy after 12 hours from symptom onset is generally regarded as not beneficial.<sup>3</sup> Likewise, this time dependent benefit has been shown in trials where primary angioplasty was performed. In the Gusto IIB cohort of 1,138 patients with acute myocardial infarction, 565 patients underwent primary angioplasty.<sup>6</sup> The primary endpoint was thirty-day mortality, which in patients treated within 60 minutes of presentation was 1%. A consistent decline in mortality benefit was seen with increasing door to balloon times. The mortality in patients treated after 90 minutes was 6.4%. In addition, data from more than 27,000 patients enrolled in the National Registry of Myocardial Infarction (NRMI-2), an industry sponsored observational registry of patients with acute myocardial infarction, showed a nearly 50% increase in mortality if more than 2 hours elapsed from arrival to balloon inflation.<sup>7</sup>

The impact of complete restoration of patency is equally important to clinical outcome and is part in parcel to the goal of therapy - early and full reperfusion.<sup>8</sup> Gibson's analysis of angiographic data from nearly 5,500 patients enrolled in fibrinolytic trials shows a clear relationship between 90-minute patency and mortality.<sup>9</sup> Short-term mortality (4-6weeks) in patients with TIMI-3 flow (3.7%) was significantly lower than in patients with TIMI-2 flow (6.1%,  $p < 0.001$ ) and TIMI-0/1 flow

(9.3%,  $p < 0.001$ ). Furthermore, recent data suggests that while epicardial blood flow is paramount, perfusion at the tissue level or microcirculation of the myocardium may be equally or more important.<sup>10</sup> TIMI myocardial perfusion grading is a new angiographic method for assessing the microcirculation. This technique allows additional risk stratification within the TIMI epicardial grade flow. In data taken from the TIMI 10B trial, myocardial perfusion was an independent predictor of mortality regardless of epicardial TIMI grade flow.<sup>11</sup> However, there is a synergistic effect between epicardial blood flow and microvascular perfusion and their relationship to mortality, the higher the flow / perfusion the lower the mortality. This finding has generated significant enthusiasm in the arena of combining thrombolytics with glycoprotein IIB/IIIA inhibitors as the latter is postulated to have a beneficial effect on the microcirculation.

**Thrombolytics -vs- Primary Angioplasty**

As one can probably surmise, the principal determinants of survival are not equally inherent to these two treatment strategies. Outlining the advantages and disadvantages of each strategy will help shed some light on the controversy faced by emergency physicians and cardiologist in determining the best treatments for their patients.

Thrombolytic therapy has a wealth of supporting clinical trial data which demonstrates a proven mortality benefit.<sup>3,12</sup> Its ease of use, rapid administration, and universal availability have made it the historical gold standard of reperfusion therapy. It requires no specialized equipment or personnel and is essentially available in any emergency setting. Unfortunately, this universal agent comes with a price, most notably bleeding complications. The most feared is intracranial hemorrhage or stroke which occurs in approximately 1% of treated patients.<sup>3,12</sup> In addition, the risk of intracranial hemorrhage increases with advancing age. There are also numerous contraindications related to bleeding risk which limits its use in certain patients. Although the speed of patency restoration for thrombolytic therapy is excellent, its extent is not. Only 50-60% of patients achieve TIMI-3 flow at 90 minutes.<sup>8</sup> Further, many patients have subsequent reocclusion and recurrent infarction, likely as a result of paradoxical activation of the coagulation cascade. This prothrombotic effect has prompted investigators to look at alternate pharmacologic strategies such as a combination of thrombolytics with glycoprotein IIB / IIIA inhibitors to potentially attenuate this effect.<sup>1,2</sup>

Strategies for reperfusion employing primary angioplasty have been gaining momentum in the last decade, encouraged by clinical trials and meta-analysis suggesting its superiority over thrombolytic therapy<sup>13,14,15</sup> as well as interventional cardiologist enthusiasm for performing the procedure. This strategy's main attributes are superior patency of the infarct related artery (90% TIMI-3 flow at 90 minutes) and low risk of bleeding complication, especially intracranial hemorrhage.<sup>16</sup> There are few contraindications and it provides the physician with immediate knowledge of the coronary anatomy. This may afford further risk stratification and in some cases of diagnostic uncertainty, may provide the definitive diagnosis. Additionally, primary angioplasty is the preferred strategy in patients with cardiogenic shock, those with acute myocardial infarction and persistent symptoms beyond 12 hours and those who fail to reperfuse with thrombolytic therapy.<sup>17</sup>

As was the case with thrombolytic therapy, not everything about primary angioplasty is positive. Its greatest detractor is its limited availability and inherent delay in mobilizing a catheterization laboratory team. In order to perform primary angioplasty the hospital must have a catheterization laboratory and skilled personnel readily available. This is the case in fewer than 20% of US hospitals.<sup>18</sup> Furthermore, the ACC/ AHA guidelines recommend that primary angioplasty be performed at high volume centers that perform more than 200 procedures per year and by individual operators who perform more than 75 procedures per year.<sup>17</sup> Thus, only a small fraction of hospitals have facilities and skilled personnel with enough experience to be proficient at this procedure. This requirement may dilute some of the robust findings of earlier trials of primary angioplasty.<sup>13</sup> Specifically, the results may only be reproducible in specialized centers geared up for primary angioplasty 24 hours a day, not in hospitals typically found in the community setting.

### Studies Comparing Primary Angioplasty and Thrombolysis

A number of trials have been performed which directly compare primary angioplasty with thrombolysis. Unfortunately, they all have relatively small sample size and utilize either different thrombolytic agents or varying doses. Most of the trials were also performed at specialized centers that perform angioplasty routinely. Nonetheless, several authors have performed meta-analysis of these trials in an attempt to determine if one strategy is superior.

In an overview by Michels et.al. the authors reviewed seven trials comprising 1,145 patients with STEMI who were treated with either primary angioplasty or thrombolysis (streptokinase or alteplase).<sup>13</sup> Those undergoing primary angioplasty had a considerable reduction in short term (= 6 weeks) mortality (OR .56, 95% CI .33-.94). There was no longterm follow up data for mortality comparisons. A review by Weaver et. al.<sup>14</sup> of 10 trials totaling 2,606 patients included the relatively larger PAMI<sup>19</sup> and Gusto IIB cohorts.<sup>6</sup> Primary angioplasty was compared to thrombolytic therapy in which 4 trials utilized streptokinase, 3 used accelerated alteplase and 3 used standard dose alteplase. Comparing primary angioplasty to thrombolytics at 30 days, mortality was 4.4% vs. 6.5% (OR .66, 95% CI .46-.94), death or reinfarction was 7.2% vs. 11.9% (OR .58, 95% CI .44-.76), and the rate of hemorrhagic stroke was 0.1% vs 1.1% (OR .07, 95% CI 0-.43). The results were similar among the varying thrombolytic agents. Again there was insufficient long-term data available for meaningful comparisons but 6 month follow-up data from Gusto IIB, which comprised nearly half the patients, showed significant attenuation of the short-term benefits ascribed to primary angioplasty.<sup>6</sup>

The Cochrane database reviewed 10 trials with a total of 2,573 patients, many of whom were included in the previous review.<sup>15</sup> Similar to earlier findings, primary angioplasty was associated with significant relative risk reduction in short term mortality (RRR 32%, 95% CI 5-50%), death or reinfarction (RRR 46%, 95% CI 30-58%) and stroke (RRR 66%, 95% CI 28-84%). Interestingly, in a subgroup analysis the authors compared results from the largest and most recent study, Gusto IIB, to the pooled analysis. The results from Gusto IIB were less impressive than the pooled data, suggesting that the mortality benefit of primary angioplasty is less impressive when performed in community hospitals, as was the case in Gusto IIB. Another possible explanation is the use of non-optimal thrombolytic therapy (strep-

tokinase or standard dose alteplase) in the other pooled trials vs. accelerated alteplase that was used in Gusto IIB.

Emergency physicians should be cautious about comparing results found in clinical trials performed in highly specialized centers to their "real world" clinical practice. Observational registries, although not true clinical trials, may provide important information about the typical clinical practice and can be used to counterbalance the potentially unrealistic findings of the aforementioned clinical trials.

Every et. al. looked at data from the Myocardial Infarction Triage and Intervention (MITI) registry comparing 1,050 patients who underwent primary angioplasty with 2,095 patients undergoing thrombolytic therapy (2/3 alteplase, 1/3 streptokinase) and found no difference in mortality out to 4 years.<sup>20</sup> Data from nearly 30,000 patients in NRM-2 showed similar results.<sup>21</sup> The authors compared 4,939 patients undergoing primary angioplasty with 24,705 patients undergoing thrombolytic therapy (92% accelerated alteplase). For patients not in cardiogenic shock, in hospital mortality was similar for both groups, 5.2% vs 5.4% as was death/non-fatal stroke, 5.6% vs 6.2%. On the contrary, patients who were in cardiogenic shock had significantly lower in hospital mortality in the primary angioplasty group than the thrombolytic group (32.4% vs. 52.3%,  $p < 0.0001$ ).

### Summary

Selecting the ideal reperfusion strategy is a daunting task for emergency physicians as is interpreting the many confusing and conflicting reports comparing thrombolytic therapy to primary angioplasty. Thrombolytic therapy offers universal availability and is easy to use but suffers from only modest reperfusion rates and inherent bleeding risk. On the other hand, primary angioplasty offers superb reperfusion rates and minimal bleeding complications but is hampered by excessive time delays and lack of availability. From the current data, primary angioplasty appears to be therapeutically more advantageous but only if readily available and performed by experienced physicians.

The ultimate decision should incorporate a strategy that provides the safest and most efficacious reperfusion in your setting. For most physicians this will be dependent upon their institutions ability and desire to provide specialized equipment and personnel needed to perform primary angioplasty.

Most importantly for the emergency physician is to be prepared. Decisions about preferred strategies should be made well ahead of time, not at the patient's bedside. In order to be effective and timely with either strategy you should have a protocol or critical pathway that outlines the decision making process as well as the steps for actual implementation of therapy. The debate over the best strategy will continue in the foreseeable future as multiple trials employing various combinations of pharmacologic agents and mechanical reperfusion have been recently completed or are underway. The results of these studies will dictate the future direction of reperfusion therapy.

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## INFECTIOUS DISEASE REVIEW

### Bioterrorism

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Because of the recent terrorist attacks in the United States there has been an increasing need for health care practitioners to have a fundamental knowledge in the agents of bioterrorism. Unlike traditional acts of overt terrorism, bioterrorism is covert. This means the effects of the attack will first be identified in the emergency department. This new threat, as evidenced by the recent exposures to anthrax, has illustrated the importance of physicians in diagnosing, treating, and educating patients on bioterrorism. The goal of this article is to set a framework for understanding the most important agents as designated by the CDC.

The CDC has categorized the many agents of bioterrorism into categories A, B, and C. The A agents are felt to be the easiest to disseminate, cause the highest mortality, and require special preparedness. B agents are felt to be second in priority, and C agents are emerging pathogens.<sup>1</sup> Category A agents include: smallpox, anthrax, botulism, tularemia, and viral hemorrhagic fever. Category B agents include: Q fever, brucellosis, glanders, alphavirus, and various food and waterborn pathogens. Category C agents are considered emerging and include: nipah virus, hantavirus, tick borne hemorrhagic fever, yellow fever, and multidrug resistant TB. The focus of this article is to review the various aspects of category A agents deemed important for the recognition of a bioterrorist threat.