PATHOPHYSIOLOGY OF ACUTE CORONARY SYNDROME (ACS)

In almost 85-90% of cases a fully occlusive thrombus in a coronary artery is the cause of S.T. Elevation myocardial infarction (STEMI). Usual path physiology is rupture of an unstable plaque attracting thrombus formation at the site of rupture. Thus a non-flow limiting vulnerable plaque ruptures and in few hours leads to thrombus laden total occlusion of a coronary artery. This is an explanation why many patients with STEMI have had no symptoms prior to their melody of acute MI. Acute Myocardial Infract AMI is still the single most important cause of death in all age group of patients above 45 years all over the world. 50% deaths due to AMI occur within one hour of symptom onset. Therefore it is important that rapid diagnosis and management is offered to reduce mortality. Majority of these deaths are due to fatal arrhythmias. Before the patient reaches the hospital several things can be done to minimize the time delay from onset of symptoms to medical contact, in EMS area. This would entail intense patient education programme, rapid transport to well equipped cardiac center and round the clock emergency medical services.

PRE-HOSPITAL MANAGEMENT

Major component of Pre hospital delay is the interval between symptom onset and call for help, which is often more than 1 hour. Call centers and emergency help lines should be set. In several countries the call centers are advised to provide patient useful suggestion such as to chew 325mg of non-enteric coated aspirin.

The other causes of delay are prehospital evaluation transportation to hospital. In India, it is quite common for the patient to wait till the symptoms worsen and even hesitancy to call for the ambulance.

What pre hospital treatment should be recommended to patients with suspected STEMI?

Apart from chewing aspirin one should establish pre-hospital fibrinolysis protocol. Selecting reperfusion strategy involves considering assessment of time from symptom onset, risk of STEMI, risk of bleeding and contraindications of fibrinolysis and time required for transport to coronary intervention facility. Several randomized trials have demonstrated the life saving benefits of initiating fibrinolytic therapy as early as possible after the onset of ischemic type of chest discomfort. The met analysis of all trials have found 17% improvement in outcome compared to in house fibrinolytic therapy.

Basically pre-hospital thrombolysis is considered because registry has consistently revealed significantly longer delay between presentation and invasive treatment, therefore STEMI patients presenting to hospital not equipped with facility of Primary Per Cutaneous Coronary Intervention (PCI) within 90 min of time period from symptom onset should undergo thrombolysis unless contraindicated.

Benefits of thrombolysis are maximum when performed within 3 hours; and since the potential of myocardial salvage is greatest in early stages of STEMI it stands to logic that thrombolysis is offered at the patients house or in mobile CCU. In the decision making fibrinolysis. ECG changes and chest comfort are at centre.

RISK ASSESSMENT FOR PATIENTS IN ACUTE PHASE OF STEMI:

Following factors predict high risk in acute case:

- Age > 75 years.
- Hypotension < 100 mm systolic.
- Heart rate > 100 /min
- Anterior STEMI or Left Bundle Branch Block.
- Diabetes Mellitus.
- Weight < 67 kg
- Time to treatment > 4 hours.

All the patients in high-risk group fair better with invasive strategy of treatment.

Sub study of DANAMI-2 showed that mortality was significantly reduced with invasive strategy of PCI. The same study showed no difference in mortality between low risk patients treated with
thrombolysis or PCI.

Restoration of normal coronary blood flow (CBF) by reperfusion of the infarct related artery is Class I recommendation, in all cases of STEMI. It reduces both early and late mortality. Reperfusion methods may be:

- Pharmacological
- Catheter based
- Surgical

A. PHARMACOLOGICAL PREFERENCE:

Thrombolysis is no doubt well-studied reperfusion option but it should be only preferred when its benefits are equivalent to invasive treatment; or logistics do not permit it with primary PCI. These are the situations where thrombolysis may be preferred are,

i. Minimal bleeding risk.

ii. Presentation of patients < 3 hours of symptom onset to a hospital without the CATHLAB.

iii. Thrombolysis is also indicated when the patient presence with symptoms within 12 hours to a hospital without cathlab and where the transport time to a hospital with a cathlab facility is likely to be more than 90 minutes.

iv. Vascular access difficulties

Thrombolysis is most effective when administered in first “Golden” hour. 33% of the patients who have achieved successful reperfusion within one hour may not show any signs of infarction scar after 3 months when studied by radio nuclear perfusion methods.

Although PCI should be available round the clock published data suggest that the best results are achieved during routine office hours.

In short thrombolysis is widely used as an option in eligible, non-high risk STEMI, especially in pre hospital setting and whereever expert primary PCI is not promptly available.

Primary PCI is generally preferred, under following conditions:

1. Availability of skilled interventionist with full fledged Cath Lab.

2. Where door to balloon time is less than 90 min or difference between door to balloon time and door to needle time is less than 60 min.

3. High risk STEMI (extensive anterior wall myocardial infarction, cardiogenic shock, Killip class III or more.)

4. Contraindication to fibrinolysis.

5. Late presentation > 3 hours after symptom onset.

6. Increased risk of bleeding and intracranial haemorrhage

7. Unconfirmed STEMI.

It is important to note that efficacy of thrombolysis is time dependent. Longer the door to needle time less is the efficiency. On the other hand efficacy of PCI is less time dependant. It therefore would be treatment of choice when patient presents 3 hours after symptom onset.

The 2004 ACC/AHA task force on the management of STEMI concluded (no changes were made in the 2007 focused update) that it is reasonable to establish a prehospital fibrinolysis protocol in settings in which physicians are present in the ambulance OR in well-organized EMS systems that have all of the following resources 6,7:

Full-time paramedics

12-lead ECGs in the field with transmission capability

Paramedic initial and ongoing training in ECG interpretation and STEMI treatment

On-line medical command

A medical director with training/experience in STEMI management

An ongoing continuous quality-improvement program

**EVALUATION OF REPERFUSION:**

Effective reperfusion reduces mortality and ischemia events. Mere patent infarct related artery with brisk flow, may not be adequate proof of tissue perfusion. It is true that inadequate recanalisation of infarct related artery with no reflow or slow flow would reflect into poor tissue perfusion. Converse is not true. Even in presence of brisk flow in infarct related epicardial artery, tissue perfusion could be poor due to micro vascular blockade. Several factors are responsible for micro vascular failure or blockage, such as sludging of capillaries by micro emboli or platelets, liberation of toxins, serotonin and tissue odema. All these contribute to blocked micro vascular circulation and failure of tissue perfusion.

Several parameters can be used to judge effective tissue reperfusion such as:

- Resolution of chest pain.
- Reperfusion arrhythmias.
- ST Segment resolution
- Myocardial contrast echocardiography.
- Complex techniques like Single Photon Emission Computed Tomography, MRI, Positron Emission Tomography etc.

1. Chest Pain: Disappearance of chest pain, associated with improved haemodynamics is the simplest marker of reperfusion. It is comparatively insensitive because even a complete infarct with no viable tissue left behind could result into resolution of pain.

2. Reperfusion arrhythmia is a weak sign of reperfusion.
3. Reduction in ST segment elevation by more than 50% in 60 to 90 minutes is very good indicator of tissue perfusion. When present, it is highly sensitive in predicting patency (90%), but its negative predictive value is low (50%).

Gibson has described myocardial blush grading during coronary angiography for evaluating reperfusion. Although this is rapidly applicable on cath table after primary PCI, but it is less sensitive as compared to myocardial contrast echocardiography.

**CATHETER-BASED REPERFUSION**

When both options are available, primary PCI seems to offer better clinical outcomes. Primary PCI results in a lower rate of early death, non-fatal reinfarction, and stroke as compared to fibrinolysis.

The benefit of PCI over fibrinolysis is evident when patients are treated early after symptom onset and increases with greater delay in presentation and remains dependent on timely implementation.

The key logistical challenge of a primary PCI strategy is the extension of this approach to hospitals without invasive services.

Failure to achieve microvascular flow, as assessed by resolution of ST-segment elevation or contrast flow by angiography, is seen with fibrinolysis (in up to around 40% of patients) and primary PCI (in around 25%).

**SURGICAL REPERFUSION**

It is not logistically possible to provide surgical reperfusion in a timely fashion. About 10 to 20 percent of STEMI patients are currently referred for coronary artery bypass grafting (CABG) for one of the following indications:

1. Persistent or recurrent chest pain despite fibrinolysis or PCI,
2. High-risk coronary anatomy discovered at catheterization,
3. A complication of STEMI such as ventricular septal rupture or severe mitral regurgitation caused by papillary muscle dysfunction.

Patients undergoing successful fibrinolysis but with important residual stenosis, who on anatomical grounds are more suitable for surgical revascularization than for PCI, have undergone CABG with quite low rates of mortality (about 4 percent) and morbidity, provided they are operated after 24 hours of STEMI. Patients requiring urgent or emergency CABG within 24 hours of STEMI have mortality rates between 12 and 15 percent. When surgery is performed under urgent conditions with active and ongoing ischemia or cardiogenic shock, the operative mortality rate rises steeply.

*Invasive management after pharmacological reperfusion*

In view of the logistical constraints of providing primary PCI to all patients presenting with STEMI, several hybrid strategies have evolved.

- **Rescue PCI**
  When fibrinolysis fails, as judged by persistent chest pain and failure of resolution of ST segment by 50% or more at 90 mins, under such circumstances rescue PCI or a fall back PCI is offered. Rescue PCI is associated with lower rates of death, heart failure, and reinfarction by 6 months.

- **Routine PCI after fibrinolysis**
  In patients where fibrinolysis has produced successful perfusion, the benefits are consolidated by offering PCI to such patients, provided the same is offered within 24 hours. The current data seems supportive of very early invasive management after fibrinolysis with reduced composite outcomes of death, recurrent myocardial infarction, and recurrent ischemia. If logistics do not permit offering PCI within 24 hours after successful fibrinolysis, it should be deferred. Subsequently, PCI may be offered at pre-discharge time or electively using ischemia driven criteria.

**Acute phase adjunctive pharmaco-therapies**

- **Antiplatelet therapies**- aspirin, clopidogrel, prasugrel.
- **Glycoprotein IIb/IIIa antagonists**- In patients undergoing primary PCI, abciximab, a chimeric monoclonal antibody fragment targeting the glycoprotein IIb/IIIa receptor, is associated with a reduction in the composite ischaemic endpoints of death, recurrent myocardial infarction, and urgent revascularization. Small molecule glycoprotein IIb/IIIa inhibitors (tiopiban and eptifibatide) have not been extensively studied, although mechanistic studies have suggested improved vessel patency

- **Antithrombotic therapies**
  Despite limited data supporting its use, unfractionated heparin remains the most common antithrombotic therapy used for the management of myocardial infarction.

Limitations of unfractionated heparin include a variable therapeutic response depending on age, weight, and renal function, and the requirement for monitoring of activated partial thromboplastin time.

Enoxaparin is a suitable antithrombotic with fibrin and non-fibrin specific fibrinolytics. Dose adjustment is necessary in patients over 75 years of age and patients with renal failure.

<table>
<thead>
<tr>
<th>Unfractionated heparin</th>
<th>Enoxaparin</th>
<th>Fondaparinux</th>
<th>Bivalirudin</th>
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<tr>
<td><strong>Fibrinolysis</strong></td>
<td>Can be used</td>
<td>Strong preference</td>
<td>Strong preference</td>
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<tr>
<td><strong>No fibrinolysis</strong></td>
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<tr>
<td><strong>Primary PCI</strong></td>
<td>Can be used</td>
<td>Strong preference</td>
<td>Strong preference</td>
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Direct thrombin inhibitors
Studies show that in primary PCI, bivalirudin reduces major bleeding as compared to unfractionated heparin with a IIb/IIIa antagonist. 30-day cardiac mortality and total mortality were reduced, suggesting this agent might be the antithrombotic agent of choice in primary PCI.

Factor X inhibition
Fondaparinux, a synthetic factor Xa inhibitor, has been found to reduce 30-day death or myocardial infarction in patients receiving fibrinolysis and in those not receiving fibrinolysis compared with unfractionated heparin or placebo. In patients undergoing primary PCI there was no benefit with fondaparinux, with an excess of catheter thrombosis noted.

Combination of antithrombotic therapies
In general, all patients should receive aspirin and clopidogrel and one antithrombin agent (unfractionated heparin, enoxaparin, bivalirudin, or fondaparinux, but not a combination). Where there is an increased bleeding risk and an invasive strategy is planned, use of bivalirudin is supported by strong data.

For patients with elevated troponin levels undergoing PCI, abciximab in addition to clopidogrel and aspirin further reduces ischaemic events.

Summary

<table>
<thead>
<tr>
<th>STEMI within 12 hours after onset of symptoms</th>
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<tbody>
<tr>
<td>Patient presenting in a hospital with PCI</td>
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<tr>
<td>Patient presenting in a hospital without PCI</td>
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<tr>
<td>Immediate transfer</td>
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<td>&lt;3 hours*</td>
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<tr>
<td>Thrombolysis</td>
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<tr>
<td>Failed</td>
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<tr>
<td>Successful</td>
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<tr>
<td>PCI ≤ 24 hours available</td>
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<tr>
<td>PCI ≤ 24 hours not available</td>
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<tr>
<td>Predischarge ischaemia</td>
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<td>Primary PCI</td>
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<td>Rescue PCI</td>
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<td>Post thrombolysis PCI</td>
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<td>Ischaemia-guided PCI</td>
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REFERENCES