Suboptimal reperfusion after primary percutaneous coronary intervention

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Suboptimal Reperfusion After Primary Percutaneous Coronary Intervention

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Abbreviations:

ACS acute coronary syndrome

AMI acute myocardial infarction

CHF congestive heart failure

CK creatine kinase

D2B door to balloon time.

DP distal protection

LVEF left ventricular ejection fraction

IC intracoronary

IS ischemic size

IV intravenous

MACCE major adverse cardiac and cerebral events

MACE major adverse cardiac events

MI myocardial infarction.

MPTP mitochondrial permeability transition pore

MRI magnetic resonance imaging

MS myocardial salvage

MVO microvascular obstruction

NSTEACS non – ST – segment – elevation acute coronary syndrome

PostC postconditioning

PPCI primary percutaneous coronary intervention

RI reperfusion Injury

RIC remote ischemic conditioning

SN sodium nitrate

STEMI ST – elevation myocardial infarction

TIMI thrombolytic ischemic myocardial infarction

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1. Abstract

Reperfusion therapy with primary percutaneous coronary intervention (PPCI) has become the gold standard for treating patients with STEMI. Despite timely reperfusion of the affected coronary artery and restoration of blood flow, suboptimal reperfusion in myocardial tissue is seen in several patients. Damage of myocardial tissue after PPCI is thought to be caused by microvascular obstruction (MVO), no-reflow phenomenon, reperfusion injury and others. To optimize myocardial salvage during PPCI, many mechanical and pharmacological agents have been developed to address these issues. The most common mechanical strategies used during PPCI are: direct stenting, mesh - covered stents, self-expanding stents, thrombectomy, distal protection devices, deferred stenting and ischemic conditioning. Pharmacological agents such as cyclosporine A, metoprolol, abciximab, nitrates, glycogen modulators, nitroprusside, and adenosine can be used as adjunctive therapy to achieve better patient outcomes. With door to balloon (D2B) times decreasing with still high mortality among STEMI patients, other issues need to be addressed such as patient - related delays, and increasing cardioprotection. Combining mechanical and pharmacological strategies still remain at an investigational stage and needs further research. In the future, evidence based medicine will change clinical guidelines on how to treat acute coronary events, which will most likely decrease long-term side effects, and mortality rates.

Keywords: suboptimal reperfusion, STEMI.

2. Sažetak

Reperfuzijska terapija s primarnom perkutanom koronarnom intervencijom (PPKI) postala je zlatni standard za liječenje bolesnika s STEMI. Unatoč pravovremenoj reperfuziji zahvaćene koronarne arterije i obnavljanju protoka krvi, suboptimalni protok krvi u miokardijalnom tkivu vidljiv je u brojnim bolesnicima. Oštećenje miokardijalnog tkiva nakon PPKI-a je uzrokovano microvaskularnom opstrukcijom (MVO), ne-reflow fenomena, reperfuzijskim ozljedama i drugim. Kako bi se optimiziralo spašavanje miokarda tijekom PPKI-a, razvijena su mnoga mehanička i farmakološka sredstva za rješavanje ovih izazova. Najčešće mehaničke strategije koje se koriste tijekom PPKI-a su: direktni stenting, mrežasti stentovi, samo ekspandirajući stentovi, trombektomija, distalni zaštitni uređaji, odgođeno stentiranje i ishemijsko kondicioniranje. Farmakološka sredstva kao što su ciklosporin A, metoprolol, abciximab, nitrati, modulatori glikogena, nitroprusid, adenozin mogu se upotrijebiti kao pomoćna terapija kako bi se postigli bolji ishodi bolesnika. U novije vrijeme se brze stize do cath - laba, ali još uvijek je visoka smrtnost među pacijentima STEMI-a, zato treba riješiti druga pitanja kao što su kašnjenja vezana uz pacijenta i povećanje kardioprotekcije. Kombinacija mehaničkih i farmakoloških strategija i dalje ostaje u istražnoj fazi i potrebna je daljnja istraživanja. U budućnosti će ´´medicina na temelju dokaza´´ promijeniti kliničke smjernice o liječenju akutnih koronarnih događaja, što će najvjerojatnije smanjiti dugoročne nuspojave i smrtnosti.

Ključne riječi: suboptimalna reperfuzija, STEMI.

3. Introduction

In this review, I will consider the causes of suboptimal reperfusion after PPCI, and look at the most recent therapeutic advancements. Acute myocardial infarction (AMI) mortality has improved the past decades but still represents a major cause of death and heart failure. AMI is caused by the rupture of an atherosclerotic plaque, causing intraluminal thrombosis resulting in partial or complete occlusion of the affected artery. The restoration of coronary blood flow by PPCI does not necessarily lead to restoration of microvascular perfusion at the tissue level. This event is associated with increased infarct size (IS), decreased ventricular function, and increased mortality. The high occurrence of suboptimal reperfusion after PPCI has led to the development of several strategies to protect the microcirculation. [(1)]

4. Mechanisms of myocardial damage

4.1 Ischemic Injury

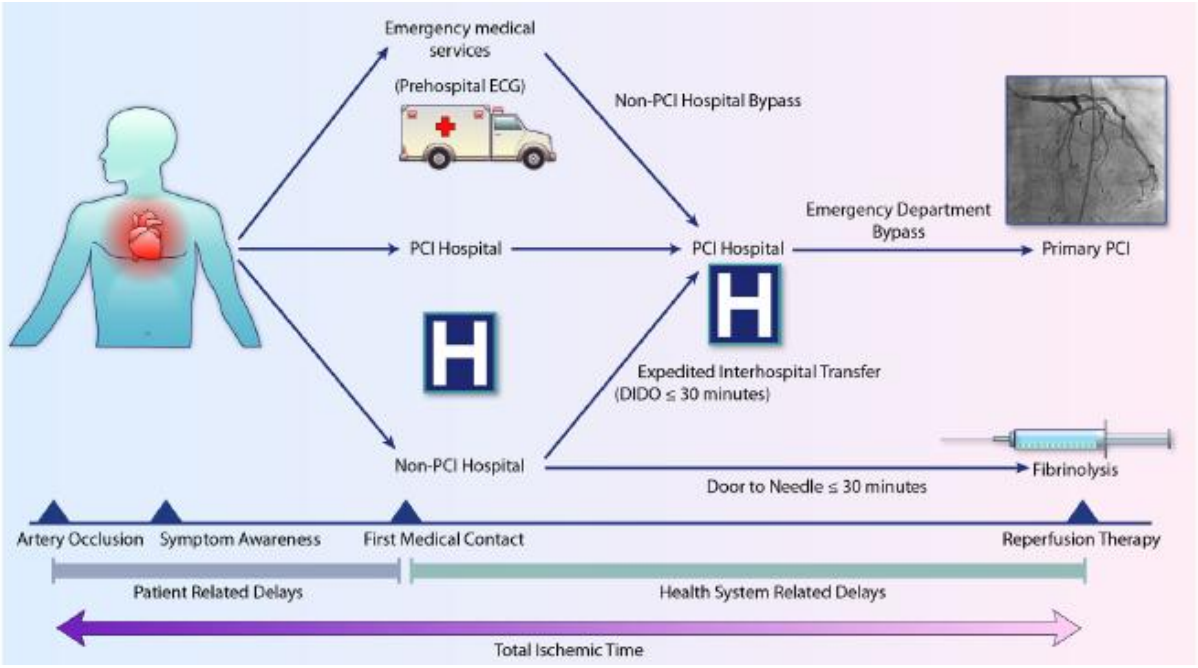
Cardiovascular disease is the leading cause of disability and death in Europe [(2)] After coronary artery occlusion there is a significant decrease of distal blood flow to the cardiomyocytes and ischemia occurs, gradually progressing to necrosis. Typically, the necrosis is complete 6 hours after the onset of the occlusion. [(3)] Patients presenting with ST – elevation myocardial infarction (STEMI) should receive timely reperfusion either by thrombolytic therapy or by PCI. Successful reperfusion treatment reduces left – ventricular systolic dysfunction, limits IS and reduces the incidence of heart failure after PPCI. [(2)]

4.1.1 Choosing the appropriate reperfusion strategy

Timely reperfusion in the occluded coronary artery is the cornerstone of treatment for acute coronary syndromes (ACS). Studies have shown continuous decrease in D2B times in the past decades, but there has been little change in-hospital mortality. To improve outcomes after ACS it is important to consider other factors such as more effective myocardial reperfusion and decreasing reperfusion injury. The American Heart Association (AHA) recommend PCI treatment over fibrinolysis if it can be achieved within 90 minutes after first medical contact. [(4)] A study showed that PCI lost its benefit over fibrinolysis if the D2B was longer than 121 minutes. [(5)] Based on these findings the American College of Cardiology/AHA guidelines for STEMI recommend PCI over fibrinolysis if it can be achieved between 90 – 120 minutes, with 90 minutes as an aim. On the other hand, fibrinolytic therapy should be applied 30 minutes after hospital presentation with STEMI, and if it is a non – PCI capable hospital and the transport to a PCI – capable

hospital exceeds 120 minutes. Strategies to decrease time to reperfusion is demonstrated in Figure 1. [4]

Figure 1. Patient-related and health-related delays during STEMI.[4]



As can be seen in figure 1, the total ischemic time is affected by the actions of the patient and health system combined. There is a potential for improvement in both patient- and health-related delays for treatment of STEMI. The patient related delays can be decreased by increasing awareness of STEMI symptoms that would urge patients to seek faster medical help. Bypassing the non – PCI hospitals, taking an ECGs before arrival to the hospital to achieve a faster response at the cath lab, and increasing PCI capable hospitals are other factors to consider.

4.2. Reperfusion Injury

Mortality from STEMI remains high and reperfusion injury may be the leading cause of this. [3] Reperfusion injury was first suggested by Jennings et al. in 1960 who reported swelling of the cell, disruption of the sarcolemma, myofibril contraction and calcium-phosphate particles in the mitochondria after reperfusion.[6,7] The benefits of reperfusion was further questioned by Braunwald et al. in 1985. who thought it might be a *double – edged sword*. [6] Recent studies have discovered the pathophysiological pathways for the damage caused by RI. After blood flow is restored, there are oxygen tension changes, an abrupt increase in intracellular concentration of Ca^{2+}, distribution of intracellular Na^{+}, and pH changes which can induce cardiomyocyte death [4]

Reperfusion injury classically includes:

• **Myocardial stunning** which is a reversible condition when the contractile function of the myocytes is impaired. This kind of RI is mainly mediated by calcium overload and reactive oxygen species.

• **Reperfusion arrhythmias** such as idioventricular rhythm, ventricular tachycardia and fibrillation. These conditions are easily treated and often self - terminate. [2,8]

• **Microvascular obstruction** (MVO) which can be caused by (i) distal embolization of debris; (ii) release of vasoconstrictor and thrombogenic factors; (iii) structural collapse of the capillary bed.

• **Lethal reperfusion;** defined as injury caused by restoration of blood flow after an ischemic episode leading to necrosis of myocytes that were previously only reversibly injured during the preceding ischemic episode. [9]

It has been very hard to prove the existence of myocyte reperfusion injury. The evidence has mostly been proven indirectly by applying therapeutic intervention at the onset of myocardial reperfusion and decreasing the IS. Based on experimental studies, it is assumed that the IS can be reduced up to 50%, suggesting that reperfusion injury may account for almost half of the final myocardial infarct size. [2]

5. Risk factors for suboptimal reperfusion after PPCI

5.1. Importance of risk factor prevention

RI in the clinical setting is defined as Thrombolytic Ischemic Myocardial Infarction (TIMI) flow grade less than or equal 2, illustrated in Table 1.

Table 1. TIMI Flow Grades [10]
Grade 0 – Complete occlusion of the affected artery
Grade 1 – Some perfusion of contrast material beyond the culprit lesion but without perfusion distally in the capillary bed
Grade 2 – Perfusion of the whole infarct affected artery in to the distal bed, with delayed flow compared to a normal artery
Grade 3 – Full perfusion with normal flow

A study from 2003, looked at the impact of suboptimal reperfusion (final TIMI ≤2 flow), which included 3,362 patients undergoing PPCI. It showed that patients with a final TIMI ≤2 after PPCI, were more likely to suffer adverse events and suffer a higher mortality in-hospital and after 1 year. The study also identified risk factors for final TIMI flow ≤2 which are summarized in table 2. [11]

Table 2 – Adjusted Odds Ratios of Clinical Variables Associated with the Risk of Final TIMI ≤2 Flow [11]

Adjusted Odds Ratios of Clinical Variables Associated With the Risk of Final TIMI ≤2 Flow

Outcome	Odds Ratio	95% Confidence Interval	p Value
Age ≥70 yrs	1.57	1.11–2.20	0.01
Diabetes mellitus	1.85	1.27–2.71	0.002
Onset of chest pain to emergency room arrival (per every hour delay in arrival)	1.11	1.06–1.17	< 0.0001
Initial TIMI ≤1	3.24	1.91–5.51	< 0.0001
LVEF <50%	1.72	1.23–2.42	0.002

Model c-statistic 0.68, Hosmer-Lemeshow chi-square = 11.4, degrees of freedom 8, p = 0.18.
LVEF = left ventricular ejection fraction; TIMI = Thrombolysis In Myocardial Infarction.

De Luca et al. showed that patients (n=1548) presenting with STEMI undergoing PPCI with congestive heart failure, described as Killip class > 1 at admission, had worse final TIMI flow grade and poorer long term outcome. [12] Killip classes I – IV classifies AMI severity, where class I shows no evidence of heart failure, and class IV are patients with cardiogenic shock.[10] Female patients with anterior MI and multivessel disease were more frequent to present with advanced Killip class, and with a higher prevalence of distal embolization [12] Studies have also shown that incomplete ST – segment resolution ((defined as ≥1 mm ST- segment elevation after PCI) had a correlation with suboptimal reperfusion after PPCI.[10]

In addition, patients presenting with unstable hemodynamic factors such as tachycardia (>100beats/min), hypotension (<100mmHg) and Killip class >1 were more frequently seen in patients with final TIMI ≤2, initially presenting as TIMI ≤1. The angiographic results also varied in patients with an end - TIMI flow ≤2 compared to patients with TIMI=3 flow. At presentation, the patient in the group TIMI ≤2 were also more likely to present initially with TIMI ≤1, left ventricular function (LVEF) < 50%, infarct in the left anterior descending artery and with a higher initial percent stenosis of the infarct artery. In this study, they used intracoronary arteriolar vasodilators such as nitroprusside, nitroglycerine, verapamil and adenosine as adjunctive therapy. These agents were applied in all patients with TIMI ≤2 flow.

Suboptimal reperfusion after PPCI is recognized as a challenge as the number of STEMI patients increases. The incidence of TIMI ≤2 flow occurs in 7, 14% of patients during PPCI. This study was important in showing that prevention of final TIMI ≤2 is crucial to prevent higher risk of further complications after PPCI. [11]

5.2 Commonly used diagnostic techniques to determine ischemic size

In the clinical setting, the IS or extent of myocardial necrosis can also be measured by biochemical markers and imaging techniques. Biomarkers commonly used are cardiac troponins and creatine kinase (CK) myocardial band. Single photon emission computed tomography (SPECT) and cardiac magnetic resonance (CMR) are common imaging techniques. However, CMR is preferred because it is found to be more accurate in estimating necrotic size and it does not cause radiation damage to the patient.[3] Other techniques shown to predict of long-term outcome after STEMI are ST – segment resolution and TIMI grade.[13]

6. Cardiomyocyte conditioning

6.1 Ischemic Conditioning

Ischemic conditioning is a term that refers to an endogenous process that protects the heart after purposeful interruptions of the blood flow in the infarct – related artery before coronary occlusion (preconditioning), after occlusion (postconditioning) or a remote organ other than the heart (remote ischemic conditioning). Preconditioning is difficult to execute because it implies application of stimuli before the occurrence of an occlusion of the coronary artery, which is almost impossible to predict. In this section, I will discuss the newest advances on postconditioning and remote ischemic conditioning.

6.2 Post-conditioning

To reduce cardiomyocyte death and increase cardio-protection, postconditioning can be used to do just this. It is performed after the culprit lesion is opened by PPCI, applying cycles of low – pressure balloon inflation before stenting. It has been associated with reduction in IS in some studies. [4] Engstrøm et al. conducted a randomized clinical trial (n=1234) where patients were randomized to conventional PCI or to postconditioning performed as 30 second occlusions repeated 4 times right after opening of the affected artery, and before stent implantation. The study failed to show a reduction in the composite outcome of all-cause death and hospitalization for heart failure. IS, MVO and ST – segment elevation differences were statistically insignificant in the two different groups.

[14] Recently, Eitel et al. conducted a randomized study to evaluate if the combination of remote ischemic conditioning (RIC) and postconditioning (PostC) (n=232) was more effective in myocardial salvage compared to PostC (+PCI) (n=232) and conventional PCI (control group, n=232). Peak CK values and ST – segment resolution were lowest in the combined group. The main finding in this trial was that RIC + PostC vs. PostC alone and conventional PCI was better in increasing myocardial salvage, that they have additive cardioprotective effects. PostC failed to show improved myocardial salvage when compared to the control group. [15]

6.3 Remote ischemic conditioning

Ischemic preconditioning is a cytoprotective strategy used to counter myocardial ischemia. [16] It has an effect like post-conditioning on the heart muscle by releasing cardioprotective circulating factors. [17] Applying repetitive cycles of ischemia-reperfusion in a tissue distant to the heart, has been associated with decreased peak troponin I levels, and greater myocardial salvage. [4]

In one study, patients were exposed to remote ischemic conditioning vs no conditioning where remote ischemic conditioning (RIC) was performed by using a blood pressure cuff to inflate and deflate the upper arm in the ambulance before reaching the hospital. 4 cycles of 5-minute inflation, followed by 5 minutes of deflation were applied to the upper arm using a sphygmomanometer. It was associated with lower major adverse cardiac events (MACE) and mortality. [4] The randomized ongoing RIC-STEMI trial is assessing if short cycles of ischemia-reperfusion to a limb will reduce the final IS before undergoing PPCI.[16] The beneficial effects of RIC have to be confirmed in bigger studies in order to be implemented in future guidelines as an adjunct to PPCI.

7. The no – reflow phenomenon

When a coronary artery is relived from severe stenosis by PCI and blood flow to the ischemic tissue remains impeded, is known as no reflow phenomenon. PPCI usually opens the occluded epicardial artery in 95% of cases, however, suboptimal tissue reperfusion often remains due to MVO leading to increased IS, remodeling of the left ventricle, and higher endpoint percentage of death. Trying to explain the no- reflow phenomenon and MVO after PPCI it is believed that distal embolization of thrombotic debris is crucial in development of this condition and subsequent clinical consequences.

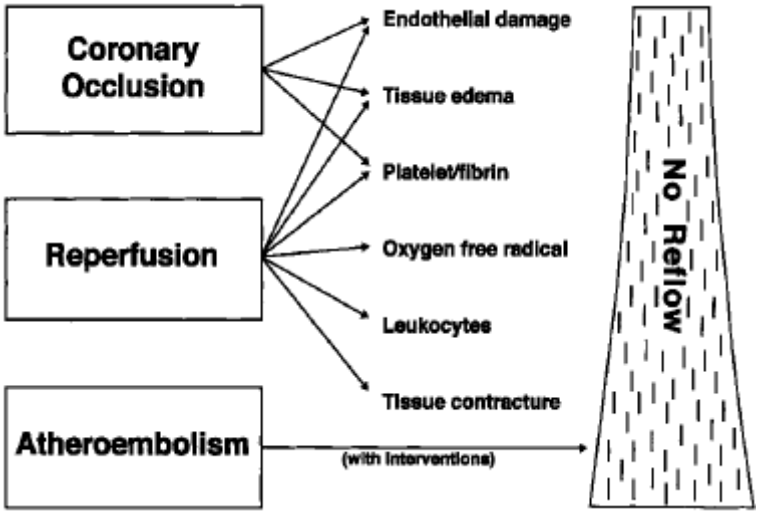


Figure 2. Various mechanisms implicated in the genesis of the no-reflow phenomenon. [18]

As seen in figure 2, the no-reflow process is influenced both by the ischemic and reperfusion period. [18]

Despite having a patent vessel and no coronary dissection, spasm nor distal macroembolus after PPCI there is a distal filling defect distal to the site of PCI. It has been suggested to be connected to microvascular dysfunction.

The incidence of no – reflow has varied a lot depending on which imaging technique was used. Some studies have shown 12 % to 25 %, while in the PAMI and CADILLAC trials the incidence was significantly lower, only 4 % to 7 %. Using myocardial contrast echocardiography has shown 34% to 39%. Factors that have been observed to affect the no – reflow are Killip class, Q wave numbers, the motion of the ventricular wall on echocardiogram, and initial TIMI flow grade 0 on the coronary angiogram. Another important predictor is the time it takes to reperfusion from symptom onset. [10] The no – reflow phenomenon strongly predicts long – term cardiac complications after AMI.[19]

Several factors are probably connected to the no-reflow phenomenon. Distal embolization of thrombotic material, damage to the microvascular bed, necrosis and stunning of the myocardium after reperfusion injury. [10] In the next sections, I will discuss mechanical and pharmacological therapeutic strategies to counter suboptimal reperfusion.

8. Mechanical strategies to enhance myocardial salvage during PPCI

Mechanical strategies such as direct stenting, mesh – covered stents, self – expanding stents, deferred stenting, thrombectomy and distal protection devices promote myocardial salvage by reducing distal embolization. [3]

8.1 Direct Stenting

Direct stenting is stenting without balloon pre-dilatation. A cohort study published in 2001 showed reduction of angiographic no – reflow (5.5% vs 12.0%; p=0.04), and reduced mortality (1.0% vs 8.0%) in the group undergoing PCI with direct stenting compared to balloon dilatation with stent implant, respectively. Another study showed reduction in TIMI endpoint (11.7% vs 26.9 %; p=0.01) and ST – segment resolution (79.8% vs 61.9%; p =0.01) among patients randomized to direct stenting compared to stent implantation after balloon predilation. In a bigger study called Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) they showed a better ST – segment resolution with direct stenting (n=698) compared to balloon angioplasty with stent implant (n= 1,830). Mortality (1.6% vs. 3.8%; p=0.01) and stroke (0.3% vs 1.1%; p=0.049) were also reduced among patients undergoing direct stenting. From the EUROTRANSFER registry, data on 1,419 patients who underwent PPCI after AMI where direct stenting (n=276), and conventional stenting (n=1143) were compared. Final TIMI grade 3 (94.9% vs 91.5%; p=0.020) and reduced risk of no – reflow phenomena (3.4% vs 1.4%; p=0.035). The mortality at 1 year was lower in the direct compared to the conventional stenting group (6.5% vs. 2.9%, p = 0.047).

Direct- compared with conventional stenting resulted in significantly greater rates of postprocedural TIMI grade 3 flow (conventional vs. direct stenting: 91.5% vs. 94.9%, adjusted odds ratio (OR) 2.09 (1.13-3.89), P = 0.020), and lower risk of no-reflow (3.4% vs. 1.4%, adjusted OR 0.31 (0.10-0.92), P = 0.035). The rates for ST-segment resolution >50% after PCI were higher in patients treated with direct stenting technique (76.3% vs. 86.2%, adjusted OR 1.64 (1.10-2.46), P = 0.016). A significant reduction in 1-year mortality in patients from the direct stenting group compared with the conventional stenting group, even after adjustment for propensity score was observed (6.5% vs. 2.9%, adjusted OR 0.45 (0.21-0.99), P = 0.047). [20]

8.2 Mesh – covered stents

Mesh covered stents trap distal embolic debris at the culprit lesion in patients with STEMI. In the MASTER (Safety and Efficacy Study of MGuard Stent After a Heart Attack) trial they randomized patients to a MGuard stent, or to a bare metal or drug – eluting stent within 12 hours of presentation with STEMI. It showed that ST - segment resolution (70% vs 57.8% vs 44.7%, respectively) and TIMI flow grade 3 were achieved more frequently in the patients receiving the MGuard stent (91.7% vs 82.9%; p=0.006). However, at 1 year the incidence of MACE were increased in the mesh covered stent group. (9.1% vs. 3.3%; p=0.02) but mortality at 1 year remained lower in the MGuard stent group (1.0% vs 3.3%; p=0.09). The trial concluded that the MGuard stent does prevent distal emboli in patients with STEMI with a high thrombus burden. Nonetheless, looking at these results, the use of MGuard stents in STEMI patients remains limited and further investigations are needed. [20]

8.3 Self – expanding stents

Underestimation of the vessel size is a well-known challenge in PCI. Self – expanding stents can adjust to the vessel itself, by gradually growing, deploying at a lower pressure compared to direct stents. This method may cause less local trauma and plaque disruption leading to less distal embolization of thrombotic content. Imaging techniques (angiography, intravascular ultrasound) after deployment of these stents showed that they expanded to the same degree as the epicardial vasodilation and appeared completely connected to the vessel wall. However, concerns have been voiced concerning optimal stent/vessel ratio, over – expansion after stent deployment predisposing for plaque prolapse, and stopping of stent expansion in calcified lesions. The experience with self – expanding stents remain limited in the PPCI setting, and further investigations are needed to conclude if they reduce distal embolizations and MVO.[20]

8.4 Deferred stenting

Deferred stenting is a two -step intervention with balloon angioplasty performed first, followed by stent implantation hours (to days) after the initial procedure. [20] Carrick et al. assessed if deferred stenting reduces no – reflow and save myocardial tissue in STEMI during PPCI. 101 patients with STEMI and ≥ 1 risk factors for no - reflow were randomized to deferred stenting (n=52) or to conventional (immediate) stenting (n=49).

The median time of deferral was 9 hours. The CMR imaging results at 6 months after the procedure showed reduced no-reflow and increased myocardial salvage in the deferred stenting group during PPCI. Many randomized trials are being performed to further determine the benefits of deferred stenting vs. immediate stenting. [21]

8.5 Cardioprotection with mechanical and aspiration thrombectomy

Thrombus removal by thrombectomy has been used in PPCI to decrease the likelihood of distal embolization in occluded coronary arteries. Using either a mechanical or aspiration thrombectomy method, where it has been assessed in many studies to see if it is superior to conventional PCI, in decreasing the chance of distal MVO, and in increasing myocardial salvage. Thrombus aspiration has been studied in many studies to see if it could reduce both MVO and decrease final myocardial IS. Using this approach has shown mixed results during the past years. [1]

In the randomized TAPAS (the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study) trial, 1071 patients were randomly divided into the thrombus-aspiration group or the conventional- PCI group before undergoing coronary angiography. If there was histopathological evidence of thrombotic material after aspiration it would be considered successful. The results of the study showed that aspiration thrombectomy during PPCI had beneficial effects on myocardial reperfusion compared to conventional PCI alone, regardless of clinical and angiographic characteristics at baseline. The results from this study agree with the findings in the randomized EXPIRA (Impact of Thrombectomy With EXPort Catheter in Infarct-Related Artery During Primary Percutaneous Coronary Intervention on Cardiac Death) trial. [1]

The EXPIRA study randomized 175 patients with STEMI undergoing PPCI to thrombus aspiration (n=88) or conventional PCI (n=87). Clinical follow – up was made at 9 and 24 months in patients to assess the occurrence of MACEs, such as nonlethal reinfarction, target vessel revascularization and cardiac death. The main finding in EXPIRA was that patients that had undergone aspiration thrombectomy had a lower incidence of MACEs at 2-year flow – up compared to just standard PCI. Occurrence of MACEs was much higher in the group not receiving thrombectomy (13.6% vs 4.5%, p=0.038). [13] However, in a prospective controlled pilot study, results showed no effect on left ventricular function. [22]

Recent studies in the field of manual thrombectomy during PPCI has not shown beneficial evidence. [20] Jolly et al. randomly assigned 10,732 patients with STEMI to manual

thrombectomy during PPCI versus standard PCI. The primary outcome was a combination of cardiovascular deaths, MIs reoccurring, cardiogenic shock or NYHA (New York Heart Association) class IV heart failure within 180 days. It occurred in 347 out of 5033 (6.9%) in the thrombectomy group vs 7.0 % (p=0.86) in the alone- PCI group. The secondary outcome, stroke within 30 days, occurred in 0.3% vs 0.7% in the conventional vs manual thrombectomy group respectively. The randomized study clearly showed the lack of efficacy of manual thrombotic aspiration and the association with increased risk of neurological complications.[23] In addition, the INFUSE – AMI randomized trial failed to show decreased IS at 30 days after PPCI using manual thrombectomy. [24]

8.6 Distal protection devices

Proximal or distal occluders, distal filters and thrombus extraction devices can be used to decrease the embolic burden at the culprit lesion in patients undergoing PPCI. The SAFER (Saphenous vein graft angioplasty Free of Emboli Randomized) trial showed that distal protection devices protect distal embolization and improve clinical outcome in bypass graft vessels. However, several trials using these devices have been unsatisfactory.[20] In the DEDICATION (The Drug Elution and Distal Protection in ST – Elevation Myocardial Infarction) trial patients presenting with STEMI within 12h of symptom onset were randomized to PCI with (n=312) or without (n=312) distal protection, using a filterwire system. The results showed that a routine use of distal protection with a filterwire system during PPCI was not recommended. It did not appear to decrease infarct size nor reduce major adverse cardiac and cerebral events (MACCE).[25]

In one study, Doppler guidewire was used to detect embolic particles during PCI in patients with AMI where visible debris has been retrieved in 73% of the patients during PPCI. The study also assessed if the embolic particles would be reduced if using a distal protection (DP) device. The conclusion was that the DP device did effectively prevent embolization in all patients in the DP – group. [26] However, it remains unknown if the DP device can reduce the embolic burden in the clinical setting. In the EMERALD (Enhanced Myocardial efficacy and recovery by aspiration if liberated debris) trial they discovered that embolic debris is liberated and may be retrieved in several patients by using the GuardWire during PPCI, DP from emboli did not improve microvascular flow, IS was not

improved nor reduce mortality. Therefore, they concluded that the routine use of GuardWire is not recommended. [27]

9. Pharmacological strategies in suboptimal reperfusion during PPCI

Pharmacological therapeutic strategies are used to reduce IS by reduction of RI. There has been done many studies on possible pharmacological therapies to prevent RI. Many studies have not been able to prove benefits of the drugs tested. In this section I will mention the most relevant pharmacological agents proven to reduce RI.

9.1 Cyclosporine A

Some studies have shown that mitochondrial permeability transition pore (MPTP) is an important element of reperfusion injury. MPTP is a downstream component in the signaling pathway involved in reperfusion injury and is becoming and target for pharmacotherapy.

Cyclosporine A is a drug that inhibits MPTP channel opening, the inhibition of MTPT is an event also observed with postconditioning. [28] A small trial (n=58) investigated if intravenous (IV) bolus of 2.5mg/kg cyclosporine administration right before undergoing PCI would limit the IS at the time of a MI vs normal saline administration. The data gathered showed that CK levels were reduced in the cyclosporine A group compared to the control group (p=0.04). Troponin levels were similar whereas the IS was lowered on day 5 using CMR in the group receiving cyclosporine A with a median of 37g vs 46g in the control group (p=0.04). [29] Despite the small study, these results showed promising therapeutic advances in decreasing IS using cyclosporine A during PPCI. Despite these results, this study was small, and a meta – analysis was done on 20 experimental studies observing pig hearts that showed heterogenic results raising concern about the cardioprotective effects of cyclosporine A in humans. [28]

9.2 Metoprolol

Ibanez et al. investigated if IV metoprolol administration immediately before PPCI decreases IS. Patients (n=270) were randomized to receive IV metoprolol (n=131) or not (n=139) before reperfusion of the affected artery(ies). The effect of beta blockers has been studied thoroughly before the era of PCI and lacked promising results. However, this trial was aiming to test the infarct limiting effect of metoprolol during PPCI. Current clinical guidelines do not include the application of metoprolol during standardized PPCI,

however, it can be applied if deemed appropriate. Patient qualified for enrollment were 18 to 80 years old, experienced STEMI for > 30 minutes and had a ST – segment elevation ≥2mm with ≤6 hours of symptom onset to reperfusion. Exclusion criteria were patients actively using beta – blockers, Killip class III or IV AMI, systolic blood pressure < 120mmHg, atrioventricular block type II or III or bradycardia. The patients were randomized to receive maximum of 5mg boluses of metoprolol tartrate 2 minutes apart. Otherwise, patients were treated in accordance to current guidelines. In addition, all patients received oral metoprolol tartrate during hospitalization in line with clinical guidelines. The mean infarct size measured by CMR was smaller after IV metoprolol (25.6g ± 15.3g) compared to the control group (32.0g ± 22.2g, p=0.012). The LVEF was improved and MACE was reduced in the drug receiving group compared to conventional PCI (7.1% vs 12.3%, respectively, p=0.21). Patients receiving IV metoprolol immediately before PCI in patients with anterior Killip class ≤2 AMI reduced IS and increased LVEF during the first day after STEMI. [30]

9.3 Glycoprotein IIb/IIIa platelet receptor inhibitors

Abciximab: The INFUSE – AMI randomized trial, used two strategies during PPCI that were previously proposed to benefit patient outcome after PPCI. They determined whether intracoronary bolus of abciximab vs no abciximab, and manual aspiration thrombectomy vs no thrombectomy would decrease distal emboli and improve patient outcome after reperfusion therapy. All patients also received bivalirudin anticoagulation undergoing PPCI. The results of the study showed that patients randomized to intracoronary (IC) abciximab compared to no drug had reduction in IS at 30 days measured by CMR (median 15.1% vs 17.9%, respectively, p=0.03). Patients undergoing PPCI with aspiration thrombectomy showed no significant difference (median, 17.0% vs 17.3%, p=0.51). They concluded that application of abciximab decreased IS whereas manual aspiration thrombectomy did not. (24) IC vs IV bolus abciximab was compared by Thiele et al. The randomized study showed that IC (n=77) vs IV (n=77) administration of abciximab during PPCI reduced the median IS (15.1% vs 23.4%, respectively) and MVO. The TIMI flow grade was the same in the two groups. [31] However, not all trials have been positive. [32]

Tirofiban:

Recent studies have researched this drug which disappointing results. Song et al. applied a high-dose of tirofiban during PPCI to assess IS vs conventional PCI. It did not show long -

term benefits. In a study, where tirofiban was administered (vs. placebo) before reaching the hospital also lacked promising results. [33]

9.4 Glucose modulators

The double blind IMMEDIATE (The Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency Care) trial randomized patients to administration of glucose, insulin and potassium (GIK) vs placebo during transfer to the hospital. This was done in patients suspected of ACS. They assessed the progression of ACS to MI within 24 hours by ECG and biomarkers. There was no difference in progression to MI between patients in the GIK – receiving group (n=200, 48.7%) vs placebo (n=242, 52.6%), however, in the subgroup of patients presenting with STEMI, the GIK – receiving group had reduced IS measured by CMR. (34) However, a meta – analysis that involved more than 28 000 patients, did not find any significant benefits with GIK therapy. [35] Further studies are needed to assess the use of GIK as pretreatment in the out-of-hospital setting for patients with ACS.

9.5 Adenosine and Nitroprusside

In the multicenter REOPEN-AMI study (intracoronary nitroprusside versus adenosine in AMI) assessed if nitroprusside or adenosine administered after thrombus aspiration would improve patient outcome. The patients were randomly assigned to 3 different groups, to receive i) adenosine (n=80), ii) nitroprusside (n=80) and iii) saline (n=80). Positive results of the study were based on ST - segment resolution > 70%, where there was 71% resolution in group i), 54% in group ii) and 51% in group iii). Furthermore, at 30 days, the angiographic MVO was significantly reduced in the adenosine group compared to the nitroprusside and controlled group (18% vs. 24% vs. 30% respectively, p=0.06 and p=0.37, respectively, vs. saline.) In addition, MACE was lower in group 1 and 2, compared to group 3. (10%, vs. 14% vs. 20%, respectively, p=0.08, and p= 0.29 vs. saline). This study showed that patients undergoing thrombus aspiration with IC injection of adenosine had significant improvement of MVO, as assessed by ST - segment resolution. Another study conducted by Parikh et al., showed that combination therapy with adenosine and nitroprusside improved coronary flow and decreased MACE if compared to adenosine alone during PPCI. [35, 36, 37]

Robert A. Kloner reviewed trials on the cardioprotective effects of adenosine during PPCI. The Acute Myocardial Infarction Study of Adenosine (AMISTAD) 1 and 2, showed that adenosine reduced anterior wall MI after a 3 - hour long administration of high dose IV infusion that was introduced at the time of PPCI. However, the drug did not significantly decrease the total congestive heart failure (CHF) in AMISTAD 2. A different sub-study showed contrary results, where in fact, adenosine did reduce overall CHF. In a prospective, double blind, single center trial, they could not find evidence supporting a high dose IC injection of adenosine to increase myocardial salvage nor decrease MVO. However, this study was limited by the small population group, and it was only done in one center. [33, 38] The Safety and Effectiveness of Nitroprusside in Preventing No-Reflow During Percutaneous Coronary Intervention: A Systematic Review study evaluated the clinical proficiency of sodium nitroprusside in preventing the no-reflow phenomenon. This meta - analysis concluded that TIMI flow was improved and incidence of no-reflow reduced. The use of sodium nitroprusside is still controversial, and no standardized clinical guidelines exist. [39]

9.6 Sodium nitrite and nitric oxide

Sodium nitrate is an arteriolar vasodilator, inhibits platelets and has anti-inflammatory abilities. The NIAMI (intravenous sodium nitrite (SN) in acute ST-elevation myocardial infarction) trial randomized 229 patients with STEMI to either intravenous SN or to placebo for 5 minutes before PPCI. CMR was performed at 6-8 days and 6 months later to assess IS. The trial showed no benefits of intravenous SN concerning reduced IS. [40] Nitric oxide inhalation in patients undergoing PPCI during STEMI, was evaluated in the Nitric Oxide for inflation to reduce repercussion injury in acute STEMI (NOMI) trial, which showed no increased myocardial salvage measured by CMR. [28]

10. Negative studies

There has been mentioned several clinical studies that showed no significant clinical improvement earlier in this review. In addition to these, some disappointing trials include: i) caldaret (vasodilator), ii) delcasertib (protein kinase inhibitor, PROTECTION-AMI trial), iii) erythropoietin (REVEAL trial) and iv) eniporide (Na+/H+ exchange inhibitor, ESCAMI trial. Limited results in i) BQ - 123 (endothelium receptor inhibitor), nicoranidil (combined nitrate and potassium - ATP channel agonist) and iii) Hyperbaric oxygen administration (AMIHOT trial). [3, 33]

11. Conclusions

In the past decade, several advancements in the treatment of STEMI have evolved. Despite of the life - saving properties of PPCI and further reductions in D2B times, it has not changed mortality rates a lot. Currently there is no strategy that is optimal for the treatment of STEMI. To improve patient outcomes, these results suggest that additional factors must be addressed. Suboptimal reperfusion after PPCI is caused by several factors such as MVO and reperfusion injury. However, increasing knowledge has enabled us to target these challenges more efficiently. A combination of mechanical strategies and pharmacological agents discussed above, may optimize treatment by improving myocardial final TIMI grade, decreasing MACE and mortality. Using adjunctive therapy with PPCI, might be the best therapeutic option for patients to further improve patient outcome during PPCI. Ongoing studies around the world will help answer some of these questions and hopefully revolutionize the treatment of STEMI.

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14. Biography

Monika Praljak is a soon to be doctor that studied at a 6-year long medical program at the University of Zagreb, in Croatia. She is of Croatian decent but grew up in Norway, Arendal, due to the Jugoslav War. Her wish to become a physician has always been a strong wish throughout her adolescent years. She finished her first year of medical school in Hungary, Debrecen and transferred to the Faculty of Zagreb after finding out about the English program there. There were also many advantages with the transfer as she had family in the area and knew the language. After spending 6 years in Zagreb, she is ready to start working in Norway and starting her career there. She has loved every moment of her medical studies in Zagreb and intends visit often.