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Myocardial Infarction: An Overview of STEMI and NSTEMI Physiopathology and Treatment

J. G. Kingma Jr

Department of Medicine, Faculty of Medicine, Université Laval, Québec, Canada
Email: john.kingma@fmed.ulaval.ca

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Abstract

Patients with myocardial infarction resulting from acute coronary syndrome are classified by electrocardiographic presentation: 1-acute ST-segment elevation myocardial infarction (STEMI) or 2-non-ST-segment elevation myocardial infarction (NSTEMI). Prompt reperfusion of an infarct-related artery by percutaneous coronary interventions provides some relief of symptoms; long-term prognosis appears to be worse in STEMI compared to NSTEMI patients but clinical findings remain controversial. Reduced myocardial perfusion to the infarct area, caused in part by microvascular obstruction, is a privileged target for diverse pharmacologic or non-pharmacologic interventions (or combinations thereof) to improve clinical outcomes. To date, benefits of both pharmacologic and non-pharmacologic strategies to either limit microvascular obstruction and myocardial injury or improve myocardial perfusion are inconsistent. This review focuses on the physiopathological aspects of myocardial infarction in relation to development of STEMI/NSTEMI and on potential cardioprotective strategies.

Keywords

Ischemia, Reperfusion, Infarction, Ischemia, No-Reflow, Microcirculation, Blood Flow, Ischemic Conditioning

1. Introduction

Myocardial ischemia that results from a perfusion-dependent imbalance between supply and demand leads to myocyte necrosis which develops progressively depending on different factors (organ, species, cardiac work, duration of ischemia, collateral blood flow, etc.) [1]. In patients with myocardial infarction, 30-day mortality rates are between 7.8 - 11.4 percent (data reported by the American Heart Association in 2015). Of these, 18 percent men and 23 percent

women (>45 years of age) succumb within a year of their initial infarction; mortality rates are worse in both sexes 5 years post-infarction and among survivors, an important cohort develop heart failure [2].

The Task Force for the Universal Definition of Myocardial Infarction, recently classified myocardial infarction to five different subtypes. Type 1 infarction occurs because of plaque rupture, ulceration or dissection, etc. in the presence of unstable atherosclerotic coronary artery disease (CAD) that comprises blood flow with resultant myocardial necrosis. Type 2 infarction is caused by a disequilibrium between oxygen supply and demand produced by factors other than unstable CAD (*i.e.* toxic effects of endogenous circulating compounds—catecholamines, endothelial dysfunction, etc.). Type 3 infarction involves patients with cardiac death resulting from symptoms associated with myocardial ischemia but for whom cardiac biomarker results are lacking. Type 4 (a and b) infarction is linked to percutaneous coronary intervention and stent thrombosis, respectively while Type 5 infarction is related to coronary artery bypass grafting [3]. Diagnosis and treatment of patients with the hope of improving clinical outcomes depend on precise classification of infarction [4] [5].

In this review, we examine clinical and experimental findings regarding the physiopathology of myocardial infarction. Scientific literature was searched using MEDLINE, PubMed and Google Scholar with the keywords myocardial infarction, ischemia, STEMI, non-STEMI, cardioprotection and various combinations thereof. Additionally, we consulted experimental findings from studies in this field emanating from our laboratory.

2. ST Segment and Non-ST Segment Elevation Myocardial Infarction

Acute coronary syndromes lead to myocyte injury and subsequent death. In the clinical setting, their classification is based electrocardiographic presentation; ST-segment elevation myocardial infarction (STEMI; ≥2 mm ST segment elevation and prominent T waves on the electrocardiogram) and non-ST-segment elevation myocardial infarction (NSTEMI; symptoms of acute coronary syndrome exemplified by ST-segment depression and T wave inversion on the electrocardiogram). Location of ST-segment changes often depends on the myocardial region affected by acute ischemia [6] [7].

STEMI is a life-threatening and time-sensitive emergency that results from complete thrombotic occlusion of the infarct-related artery [8]; these patients generally present with severe chest pain and large myocardial risk areas. Rapid access to coronary revascularization strategies are recommended and lowering door-to-balloon times remains a priority for these patients [9]. Short-term mortality risk is high in approximately 30 percent of patients with STEMI. In the remaining 70 percent of cases the risk of mortality is >5 percent [10]. Zahn *et al.* [11] reported significantly higher in-hospital mortality in STEMI compared to NSTEMI patients. Interestingly, mortality risk may be lower 2 years after hospi-

tal discharge in older STEMI patients [12]. Gender-related differences regarding clinical outcomes in female patients with STEMI and NSTEMI are not well documented but mortality in females with total coronary occlusion may be less than in men [13].

Questions remain regarding involvement of single or multi-vessel disease in these patients since they are important considerations for coronary interventions. Presence of multi-vessel disease is an independent risk factor for adverse cardiac events [14]; gender and smoking are also important risk factors [15].

Patients with NSTEMI generally present with a more heterogeneous condition (*i.e.* reduced coronary artery blood flow without complete coronary occlusion, coronary artery spasm, coronary embolism, myocarditis, etc.) but have a higher long-term mortality risk due to prevalence of comorbidities and multi-vessel coronary artery disease [16]. Tuohinen *et al.* studied the relation between electrocardiogram changes and echocardiographic findings in NSTEMI patients [17]; they reported that T-wave inversions depended on anatomic distribution of myocardial ischemia and were associated with variations in systolic cardiac function. Conversely, ST-segment depression did not correlate with areas of wall motion abnormalities (on echocardiography) but was associated with global and regional alterations in diastolic function. Physiopathological mechanisms responsible for these observations require clarification; in animal studies, subendocardial ischemia produces LV diastolic dysfunction characterized by increased LV end-diastolic pressure and diminished LV chamber compliance [18] [19]. Causes of T-wave inversion in NSTEMI are likely multifactorial being associated with total occlusion of an infarct-related artery accompanied by transmural infarction [20]; patients with an existing infarct might be beyond the stage of ST-segment elevation and only present post-ischemic T-wave inversion [17] [21]. In STEMI patients, T-wave inversion is associated with complete restoration of coronary perfusion [22]. Clearly, long-term prognosis in NSTEMI compared to STEMI patients remains the subject of debate; for example, the Global Registry of Acute Coronary Events (GRACE) study reported lower post-discharge mortality in STEMI versus NSTEMI patients [23] whereas others report the opposite [24].

3. Myocardial Infarction

Infarction produces necrosis characterized by loss of myocardial structure and cell death; this is followed by tissue repair including formation of scar. Different categories of myocardial necrosis (coagulation, colliquative and coagulation myocytolysis) are described in human and experimental studies [25] [26] [27]. *Coagulation necrosis*, the most common form, is principally but not exclusively caused by marked reductions in coronary perfusion and is characterized by loss of myocardial contractile properties (due to intracellular acidosis). *Colliquative myocytolysis* (*i.e.* liquefaction necrosis) is portrayed by lysis of myocardial fibers ensuing from release of hydrolytic enzymes by inflammatory cells (*i.e.* leuko-

cytes, neutrophils, etc.). Lesions comprise loss of contractile proteins, vacuolization, edema and nuclear changes including fragmentation. *Coagulative myocytolysis* results from the action of toxins such as nicotine and carbon monoxide; histopathological features resemble those produced by sympathetic nervous system stimulation and catecholamine release [28] [29] [30].

Infarcts are generally classified on the basis of size—microscopic (focal necrosis), small (<10% of LV), medium (10% - 30% of LV) or large (>30% of LV); however, they are also classified on the basis of location (anterior, lateral, inferior, etc.) [1]. In addition, within the pathologic context, "acute, healing or healed" infarction should be used; in acute infarction inflammatory cells are present. In healed infarcts (*i.e.* 5 - 6 weeks post-infarction), scar tissue is manifest while inflammatory cell infiltration is absent and electrocardiographic morphology remains in flux.

Acute ischemic injury is classed as being either *reversible*, where myocytes survive ischemic durations <15 minutes, or *irreversible*, with no capacity for myocyte recovery. Early restoration of blood flow to reversibly injured myocytes is key to complete recovery of cellular function with no discernable sequelae. On the other hand, irreversible myocyte injury (*i.e.* necrosis) produces marked cellular ultrastructural changes such as cell swelling, denaturation of intracellular proteins, membrane disruption, presence of contraction bands and mitochondrial calcification, etc. due to metabolic failure and rapid depletion of high-energy stores [31] [32] [33]. Other modes of cellular injury and death (*i.e.* apoptosis, autophagy, oncosis) also merit attention. Conditions that control transition from one status to the other are widely debated [34] [35].

Recently, Jennings suggested that "*myocytes are irreversibly injured when they fail to survive after restoration of the environment to normal*" [36]. Timing of cell injury and location across the myocardial wall are also important criteria; for the most part, potentially salvageable myocytes are localised in the mid-myocardial and epicardial layers. This observation led to the realization that ischemia-induced myocyte injury follows a transmural gradient across the ventricular wall following acute coronary occlusion [37] [38]. Earlier studies also hypothesized that distinct states of flow reduction and ischemic injury affect myocyte vulnerability to damage [39] [40]. These conditions are important as successful reperfusion therapy necessitates that rapid restoration of blood flow be achieved to impede development of a transmural infarct. It is important to remember that during ischemia significant damage also occurs at the level of the coronary microvasculature (*i.e.* coronary collateral vessels) that affects functional recovery of diverse cellular components of the myocardial architecture; thus, failure to restore adequate blood flow can be caused by microvascular dysfunction. In addition, while myocytes comprise more than eighty percent of ventricular mass, other cell types integral to cardiac function (*i.e.* intra- and extra-cardiac sympathetic/parasympathetic neurons) are negatively affected by ischemia; however, their injury threshold is not well established (cf. reference

[41] for additional discussion). Cardiocytes and cardiac neurons conceivably share common survival pathways; however, this remains to be proven [42]. Neuron plasticity in the cardiac neuraxis might be critical for post-infarction recovery of cardiac function [43] [44]. Interestingly, viable nerves that course over an infarcted region tend to remain so since oxygen and energy needs can be fulfilled via blood from extracardiac sources [45].

Myocyte death produced by reperfusion rather than the preceding ischemia is also possible [46]; however, no clear consensus is available regarding its existence. Potential examples of reperfusion injury include myocardial and vascular stunning, no-reflow and reperfusion arrhythmias. In NSTEMI patients, reperfusion injury may result from tissue oedema [47] [48]. Heyndrickx *et al.* reported that reversibly injured myocardium contracted less efficiently after reperfusion of the infarct-related artery [49]. During coronary occlusion opening of coronary collateral vessels in conditioned myocardium is associated with a marked reduction of ST segment elevation during repeated coronary occlusions [50] [51] [52]. However, Tomai *et al.* [53] could not confirm these findings during coronary angioplasty in patients with STEMI. Inability to show a positive relation between myocardial tissue viability and improved microvascular blood flow post-ischemia may be due to the lack of sensitivity of currently employed techniques to measure spatial distribution of blood flow within the deeper myocardial layers. Animal studies to evaluate recruitment of coronary collateral circulation are sparse; however, one study of ischemic conditioning in rabbits documented a trend to improved microvascular blood flow [54].

4. No-Reflow

A crucial factor for survival in STEMI patients is the early restoration of blood flow to the infarct-related epicardial coronary artery; this can be accomplished with primary percutaneous coronary interventions (PCI), stenting and early thrombolysis, which are essential for limitation of myocardial necrosis and maintenance of LV function. No-reflow in the heart (it can also occur in other organs) is defined as an inability to restore blood flow to previously ischemic myocardium even after return of infarct-related epicardial coronary artery patency due to microvascular obstruction (cf. recent review by Kloner *et al.* [55]) [56] [57]. This dynamic process is produced by ultrastructural alterations of vascular endothelium, platelet aggregation, inflammation, embolization by atherosclerotic plaque and thrombotic debris, etc. [58] [59] [60]. In animal experiments (using Thioflavin S or carbon black injected at the end of the reperfusion period), no-reflow zones appear to be confined within the anatomic risk zone and to areas that display myocardial necrosis [56]. No-reflow does not cause myocyte death; however, it is associated with altered healing (*i.e.* thinner scar formation) and infarct expansion, which ultimately affect ventricular function. Limited perfusion (after restoration of infarct-related artery patency) within the anatomic risk zone ultimately reduces accessibility of inflammatory

cells (*i.e.* macrophages, neutrophils, etc.) that are involved in removal of cellular debris and delivery of a multitude of endogenous factors that are required for post-ischemic remodeling of compromised myocardium [61] [62]. The absence of microvascular obstruction results in improved LV function and reduced mortality [63] [64]. In general, therapies that reduce infarct size also reduce no-reflow zone size; however, some interventions (*i.e.* oxygen radical scavengers) may benefit no-reflow independently of their effect on infarct size [65].

No-reflow has been reported in humans after reperfusion therapy for STEMI using different imaging techniques [60] [66] [67] [68] [69] [70]. This is important as the presence of no-reflow can jeopardize clinical outcomes independent of infarct size [66] [68] [69]. Major differences in physiopathology of no-reflow exist between animal and clinical studies. For the most part, animal studies use models of non-atherosclerotic coronary arteries; however, in patients angioplasty or stent deployment within a ruptured atherosclerotic plaque produces debris (*i.e.* microemboli) that result in downstream vascular obstruction over and above that produced by endothelial swelling and disruption [71]. Interventions such as mechanical thrombectomy (*i.e.* during catheterization), pharmacology (*i.e.* calcium channel blockers, adenosine, platelet aggregation blockers, anti-thrombotics, etc.) and manual aspiration of thrombus all appear to affect myocardial perfusion and clinical outcomes [72] [73] [74].

Pathogenesis of microvascular obstruction (MVO) between STEMI and NSTEMI patients may not be the same. Prevalence of MVO is markedly lower in NSTEMI compared to STEMI patients [75] [76]. Some evidence suggests that infarcts are smaller in NSTEMI patients. Reasons for the observed differences are unclear; however, an independent association between extension of MVO and infarct size exists [47] [77] [78]. Culprit vessel involvement (*i.e.* for ischemia) might also be an independent predictor of MVO; Guerra *et al.* [75] showed that the left circumflex artery was more frequently implicated in NSTEMI (versus STEMI [79]); considered as additional proof for the existence of transmural myocardial necrosis despite minimal presence of electrocardiographic criteria.

A recent meta-analysis (*i.e.* comprising seven randomized clinical trials) report from de Waha *et al.* examined the relation between MVO within the first 7 days of reperfusion and subsequent all-cause mortality, hospitalization for heart failure and re-infarction within a year follow-up in patients with STEMI [80]. They showed that MVO was independently predictive of all-cause mortality even after adjustment for infarct size; however, MVO could not independently predict re-infarction after PCI in STEMI patients. Baseline determinants of MVO such as TIMI (thrombolysis in myocardial infarction) flow, symptom-to-device time, infarct location, etc. correlated strongly with mortality. Physiopathological mechanisms for adverse impact of MVO on clinical outcomes are multifaceted and include post-infarction remodeling, inflammation, ventricular healing, etc. In animal studies, MVO is associated with increased myocardial stiffness and reduced elasticity; over time, these factors are allied with increases in wall stress

and wall thickening [81] [82]. On the other hand, absence of MVO results in marked improvement of LV ejection fraction over time [63] [64] [82]. Based on these findings, it would be reasonable to hypothesize that interventions that limit MVO potentially ameliorate clinical outcomes.

5. Protection Strategies—Non-Pharmacologic

Application of multiple, brief cycles of nonlethal ischemia and reperfusion prior to a prolonged ischemic event significantly delays progression of cell death [83]; ischemic conditioning performed before, during or after acute ischemia has been evaluated in a host of animal species but protection only occurs when reperfusion is present [84]. Cellular protection is documented in most species; however, results in humans are variable [85] [86]. Proof-of-concept clinical studies using remote ischemic conditioning (*i.e.* transient cycles of ischemia/reperfusion in a distal organ) have shown considerable potential to limit organ injury [87] [88] [89] [90]. In STEMI patients, remote ischemic preconditioning diminishes troponin I release (24 h post-PCI), chest pain and ST-segment deviation on the electrocardiogram [91] [92] [93]. Remote ischemic conditioning also improves endothelial function in patients with acute myocardial infarction when applied prior to primary PCI [94]; other studies put forward that this intervention leads to persistent protection and potential reduction of long-term clinical events [95] [96] [97]. McLeod *et al.* recently completed a meta-analysis of randomized controlled clinical trials (over 1200 patients enrolled) that compared PCI with, and without, remote ischemic conditioning in STEMI patients; they determined that remote ischemic conditioning was a promising adjunctive treatment for prevention of reperfusion injury [98]. Interestingly, maximum benefit from remote conditioning occurs in patients with the greatest degree of cardiac ischemia (*i.e.* TIMI; 0 - 1 flow) [99]. The CONDI2/ERIC-PPCI trial, a randomized controlled clinical study, is currently ongoing to evaluate whether remote ischemic conditioning can reduce cardiac death and hospitalization for heart failure at 12 months in patients presenting with a ST-elevation myocardial infarction and treated by percutaneous coronary intervention [85]. While remote conditioning is a promising adjunctive treatment to PCI to limit reperfusion injury, further studies in different patient cohorts are necessary to secure its status as a legitimate cardioprotective therapy. Innate ischemic preconditioning could occur within the context of pre-infarction angina and exercise-induced ischemia. Pre-infarction angina mitigates ischemic injury by triggering endogenous intracellular signalling pathways [100]; exercise ischemia (*i.e.* warm-up angina) is reported to occur consequent to an increase in metabolic efficiency and not by improvements in myocardial perfusion [93] [101].

6. Protection Strategies—Pharmacologic

Pharmacologic interventions administered at the time of PCI also improve clinical outcomes in STEMI patients. Recently, Bullock *et al.* reported significant

improvement of clinical outcomes in STEMI patients given intracoronary adenosine as an adjunct to reperfusion [102]; these findings contrast with earlier meta-analyses of randomized control clinical trials, which failed to document clinical benefit in patients with STEMI [103] [104]. Benefits of intracoronary adenosine treatment were associated with improved myocardial perfusion; interestingly, administration via the intravenous route provided no positive effects (cf. AMISTAD-II study) [105] [106]. Adenosine is a potent vasodilator with anti-inflammatory properties that contribute to reduce microvascular obstruction (due to neutrophil adhesion and migration, antiplatelet effects, etc.) and diminish risk of adverse cardiac remodeling [107] [108] [109]. In experimental studies, adenosine (dose-dependent) limits ischemic injury; however, questions remain regarding efficacy with adenosine administration at the time of reperfusion [108] [110]. In humans, the REFLO-STEMI trial examined effects of intracoronary adenosine (and other vasodilators) on infarct size and microvascular obstruction [111] [112]; results indicate that adenosine did not limit infarct size or reperfusion injury when administered during PCI but may (at higher dosages) cause cardiac toxicity with worse clinical outcomes. In a recent study from Zhou and co-workers, combination therapy (atorvastatin, IC adenosine, tirofiban, thrombus aspiration) in addition to PCI had a markedly lower incidence of no-reflow and improved prognosis in STEMI patients with a high risk of no-reflow [113]. Several pre-clinical and clinical studies have examined combined therapy approaches with inconsistent results [99] [114] [115]; further investigation using combined reperfusion therapy and pharmacologic compounds that target pro-survival pathways is necessary.

Pharmacologic compounds currently focused on protecting against post-ischemic vascular injury and no-reflow in STEMI patients include statins, ß-blockers, cyclosporine, nicorandil (K_{ATP} channel agonist), exenatide and liraglutide (GLP-1 analogues) [116]-[122]. Non-steroidal anti-inflammatory drugs have also been studied but their efficacy in STEMI and NSTEMI patients is inconsistent [123] [124] [125]. The relation between platelet activation/aggregation and major adverse cardiovascular events in STEMI and NSTEMI patients has also been investigated in numerous clinical trials (DISPERSE, PLATO, APELOT, ONSET/OFFSET, etc.) [126] [127] [128]. Use of P2Y12 antagonists such as prasugrel, clopidogrel, ticagrelor, etc. have been studied; benefit-to-risk ratio balance with these drugs remains a concern because of an increased risk of ischemic complications [129] [130] [131].

7. Summary

Understanding the physiopathological mechanisms associated with development of myocardial injury after acute coronary artery occlusion is imperative for elaboration of effective therapeutic interventions (pharmacologic, non-pharmacologic, combination therapy) to improve clinical outcomes in STEMI and NSTEMI patients. The ability to specifically target reperfusion injury in acute coronary syndrome patients

could enhance capacity to reduce the adverse consequences of myocardial infarction. More information is needed regarding pathogenesis of cardiac injury in patients with comorbidities, co-medications along with age and gender differences.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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