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Review Article

Diastolic Dysfunction following Acute Myocardial Infarction with ST Segment Elevation

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ABSTRACT

Reperfusion is a critical component of myocardium survival in acute myocardial infarction to minimize infarct ST segment elevation myocardial infarction (STEMI) caused by atherosclerotic vulnerable plaque rupture or plaque erosion, resulting in activation of the coagulation cascade. It causes a temporal sequence known as the "ischemic cascade," which first involves the metabolic process, the diastolic dysfunction, and then systolic dysfunction. Diastolic dysfunction in STEMI patient is an independent predictor for long-term outcome. Rapid and early restoration of blood flow is critical to ensure cell recovery and prevent additional damage.

1. Introduction

The incidence of ST-segment elevation myocardial infarction (STEMI) has increased in developing low-income countries, while it has declined in developed high-income countries in recent decades.[1] According to the American Heart Association, the prevalence is 3% in the United States.[2]

Acute myocardial infarction mortality has fallen from 20% in the late 1980s to 5–7% in normal practice in the United States and Europe, with considerable regional variability owing to differences in use and manner of reperfusion.[1] The average 30-day mortality following acute myocardial infarction was 13.6 percent in 2018, which included 2363 institutions. Rural hospitals had higher mortality.[3] Large infarct area, late hospitalization, and the lack of tissue-level reperfusion after revascularization remain etiology for mechanical complications, hemodynamic instability, and pump failure.[2]

2. Atherosclerotic in Culprit lesion

Many plaques of the culprit lesion in patients with acute coronary syndromes are vulnerable to rupture, according to findings from intracoronary imaging and pathology studies. It has characterized lesions as thin-cap fibroatheromas at risk for recurrent events. The lesions ha have lipid-rich core and thin cap thickness (< 65 µm), large plaque load and vessel external remodeling.[4]

Inflammation and subsequent thrombotic complications are caused by activated T cells and macrophages located in the central lipid core, tunica intima, and media.[4] Monocytes are recruited to increasing atherosclerotic plaques, and then differentiate into macrophages. It is due to the retention within the subendothelial layer of low-density lipoprotein (LDL). Macrophages maintain inflammation and destabilize the endothelial layer and the extracellular matrix.[5]

Collagen is necessary for the fibrous cap's integrity. Its synthesis is inhibited by interferon gamma, and its breakdown is accelerated by metalloproteinases, an interstitial collagenase produced by macrophages. As a result, the plaque's surface weakens gradually and eventually ruptures. Low shear stress also promotes plaque growth and fibrous cap thinning.[4] Plaque evolvement as a result of the rapid necrotic core expansion is also caused by repeated intraplaque hemorrhage, which increases free cholesterol deposition and macrophage infiltration. A continuous inflammation cycle, degradation of extracellular matrix, and remodeling expansion can result in acceleration of plaque growth and, eventually, acute disruption of the plaque.[5]

3. Plaque Rupture and Activation of the Coagulation Cascade

Rupture of the high-risk vulnerable plaque, allowing highly thrombogenic core and matrix components to enter the circulatory system. The tissue factor is a powerful coagulation cascade inducer.[6] The platelets begin to attach to the revealed subendothelial matrix. The activated platelets change its form and release different bioactive chemicals, including ADP. ADP then activates platelets by stimulating P2Y purinoceptor 12 (P2Y12), an ADP receptor.[5]

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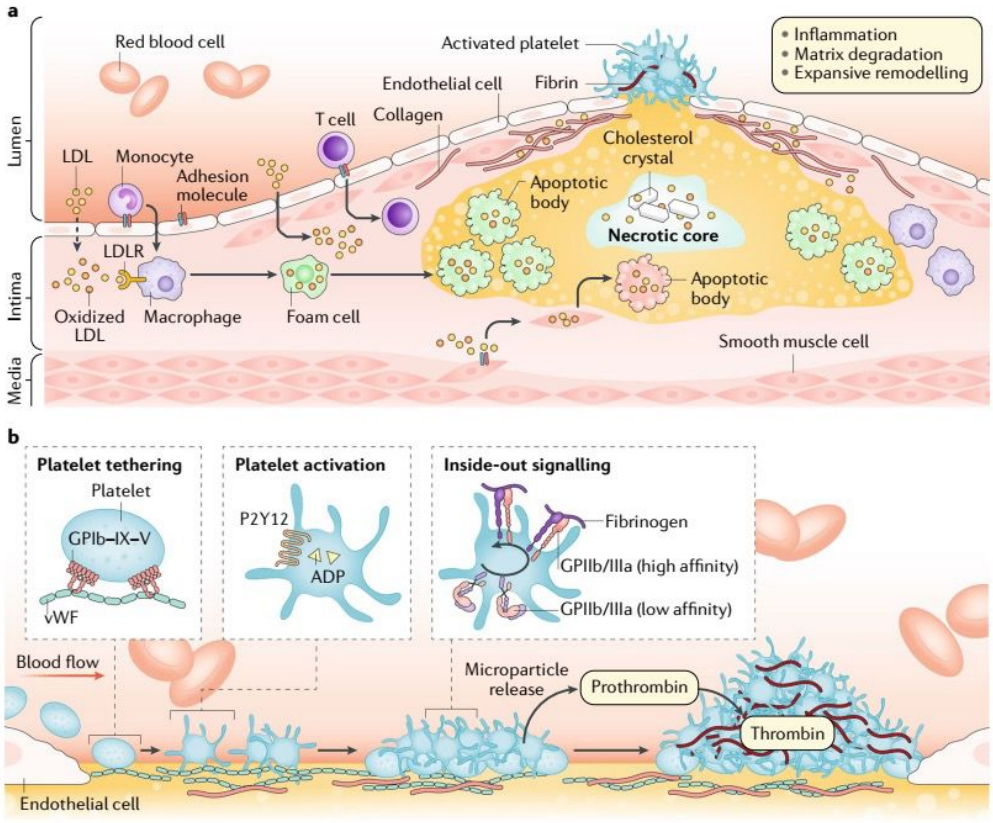

Figure 1. Atheromatous plaque development, plaque rupture and thrombus formation.[5]

After activation of platelet, the fibrinogen receptor GPIIb/IIIa changes in a highly affinity ligand binding state. The last common pathway for platelet aggregation is mediated by GPIIb/IIIa receptors. Excessive activation of the platelet leads to thrombin production. Several thrombin receptors on the platelet are activated effectively by the thrombin, which activates the platelets further. Fibrinolytic system is also inhibited by inflammation. Inflammation promotes the synthesis of fibrin, which constitutes one of the primary thrombus components,

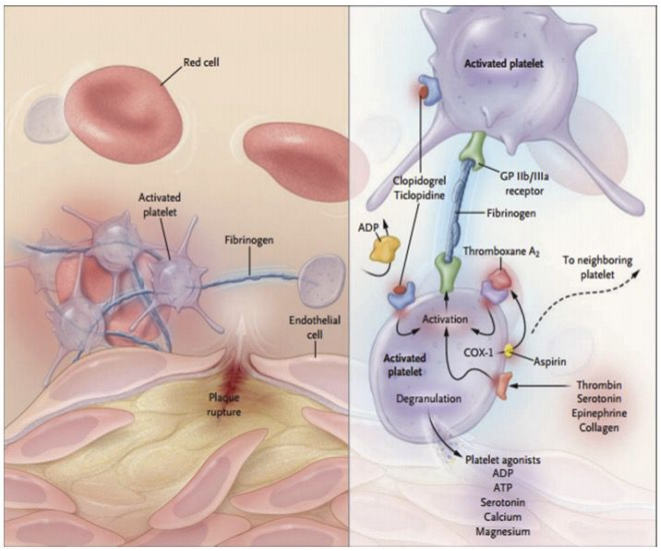

Figure 2. The activation of platelets and coagulation. ADP, adenosine diphosphate; COX-1, cyclooxygenase-1; GP, glycoprotein.7

and produce the plasminogen activator inhibitor 1 (PAI1), the main fibrinolysis endogenous inhibitor.[5]

Acute coronary syndrome has also been linked to superficial erosion. Those that lay under the surface of the erosion do not have thin fibrous caps. They have fewer inflammatory cells, smaller lipid pools, and an abundance of extracellular matrix, particularly proteoglycans and glycosaminoglycans. Erosion is more often associated with NSTEMI than STEMI.[8] Plaque erosion was strongly related with age 50 years, current smoking, absence of additional coronary risk factors, lack of multi-vessel disease, decreased lesion severity, bigger artery size, and adjacent bifurcation.[9]

4. Ischemia of the Myocardium

Myocardial ischemia produces significant changes, which often occur in a time sequence known as the "ischemic cascade," which affects the metabolic process first, then the mechanical, and lastly the electric cells of the myocardium.[10] After cardiac perfusion is suddenly interrupted, the anaerobic metabolism, reduction of high-energy phosphates, and the anaerobic glycolysis occur. Anaerobic glycolysis converts glucose to lactic acid. As a result, free fatty acids are produced, and mitochondrial K-ATP channels are inhibited, making it impossible to maintain membrane potential of mitochondria.[10]

During acute myocardial ischemia, an increase in protons causes intracellular pH to drop to <7.0 due to anaerobic glycolysis. Because of ATP depletion, intracellular protons stimulate the Na+/H+ ion exchanger while decreasing Na+/K+ ATPase activity, resulting in intracellular Na+ overload. As a consequence, the Na+/Ca2+ ion exchanger operates in reverse mode to remove excess Na+, but this causes intracellular Ca2+ overload.[12]

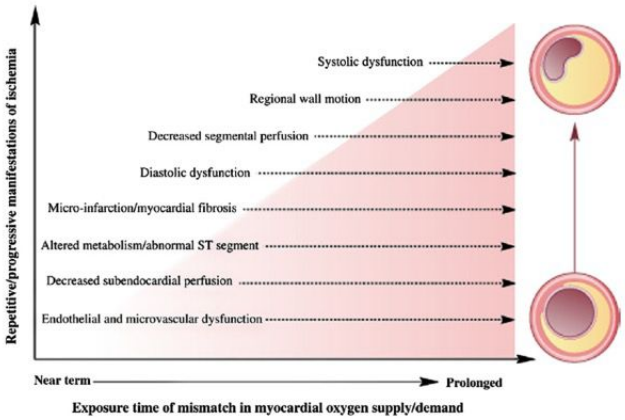

Figure 3. Cascade of mechanisms and manifestations of ischaemia.[11]

Reduced ATP availability decreases sarcoplasmic reticulum Ca2+ intake as well as Ca2+ extrusion from the cell. The increase in intracellular Ca2+ causes a Ca2+ excess in mitochondria, which further reduces ATP synthesis. The Ca2+ therefore plays a critical part in the malevolent cycle that results in cell damage in the event of persistent ischemia.[10]

Abundance intracellular calcium enters the mitochondria, causing overload of mitochondrial calcium, which inhibits ATP generation, aggravates energy metabolism problems, and ultimately leads to myocardial cell death. Mitochondrial damage is thought to be an indication of cardiac cell transition from reversible to permanent damage.13 At this point, the mitochondria are enlarged, and since they are unable to regulate their volume, the endothelium pattern stays dilated, with increased the level of water, and also sodium and potassium chlorides. Severe ischemia causes contractility loss due to the significant reliance of cardiac function on oxygen.[10]

Phospholipases which degrade the skeleton of the cell membrane, namely protein kinase C and phospholipase A, may also activated by intracellular calcium. Furthermore, the process generates a number of harmful chemicals, including free fatty acids, leukotrienes, prostaglandins, and oxygen-free radicals. These disrupt mitochondrial function, increase membrane permeability, obstruct cell signal transmission, and induce widespread cardiac cell apoptosis. Excess calcium may also activate caspase, calpain, and endonuclease, all of which promote intracellular protein and fat digestion.[13]

5. Infarction of Myocites

A myocardial ultrastructural changes, cellular and mitochondrial enlargement, and glycogen depletion are theoretically reversible; nevertheless, just one acute ischemia lasting at least 20-30 minutes causes permanent damage, including cardiomyocyte necrosis. The breakdown of the integrity of the sarcoplasmic membrane during the early stages of myocardial necrosis enables intracellular molecules to migrate to the cardiac interstitium and subsequently into circulation.10 Early ischaemia is characterized by abnormal wall motion or oedema.[4]

Early ischaemia is characterized by abnormal wall motion or oedema.[4] The cytoplasmic membrane is severely damaged as a result of mitochondrial enlargement. This is proof of the lesion's irreversibility and may be seen after 30-40 minutes of ischemia. The most internal wall is permanently destroyed after 60 minutes. Necrosis occurs within 6 hours after the start of acute severe myocardial ischemia.10 Myocardial infarctions develop as a wave of necrosis that extends from the sub-endocardium to the sub-epicardium during a 3- to 4-hour period.[6]

Infarcts are categorized into three types based on their pathologic appearance: acute (6 hours to 7 days), healing (7-28 days), and healed (29 days or more). The presence of polymorphonuclear leukocytes characterizes an acute or developing infarction. If the time between the start of the infarction and death is short, there may be few or no polymorphonuclear leukocytes. A healing infarction shows the presence of mononuclear cells and fibroblasts and the lack of polymorphonuclear leukocytes. Scar tissue without cellular infiltration characterizes a healed infarction. The whole process of healing an infarction typically takes 5 to 6 weeks or more. 6 Lessen the time between ischemic myocardium and reperfusion in STEMI patients is important for salvaging ischemic myocardium, limiting residual damage, lowering the risk of future heart failure, and improving survival. The reperfusion within 60 to 90 minutes after ischemia start results in the most efficient rescue of myocardium. The first 60 minutes of infarction has been known as the "golden hour" because restoring myocardial function is best accomplished during this time, and some patients even experience aborted infarction without evolving electrocardiographic changes and without mechanical deficiency.[19]

The inflammatory phase is characterized by infiltration of immune cell that absorbs and removes damaged cells and extracellular matrix tissue, accompanied by a reparative phase characterized by inflammation resolution, (myo)fibroblasts proliferation, scar formation, and neovascularization over the next several days. Hypoxia affects vascular endothelial cell integrity and barrier function, increasing vessel permeability and promoting leukocyte infiltration.[14]

Rapid neutrophil degranulation and degradation have been shown to play a significant pro-inflammatory role, inducing cardiomyocyte death, contributing to an increase in infarction size (so-called "neutrophil-induced injury"), and impairing wound healing.[15]

Larger infarcts with more severe inflammatory activation, on the other hand, show increasing ventricular dilatation and heart failure over time, with ongoing inflammation and infiltration of tissue immune cell. Chronic inflammation may be the result of lack of inflammation

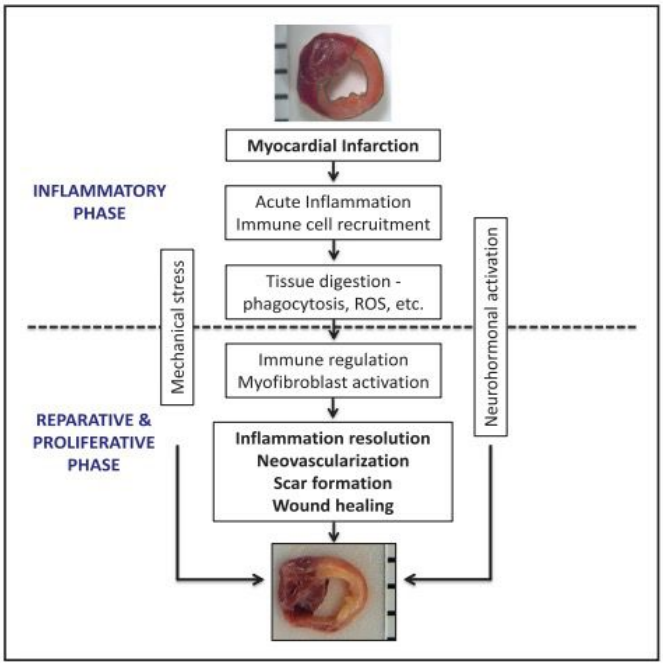

Figure 4. Cardiac repair after MI. Tissue damage and necrosis begin the inflammatory phase. Then the phase changes to a reparative and proliferative phase in murine models, resulting in healing.[14]

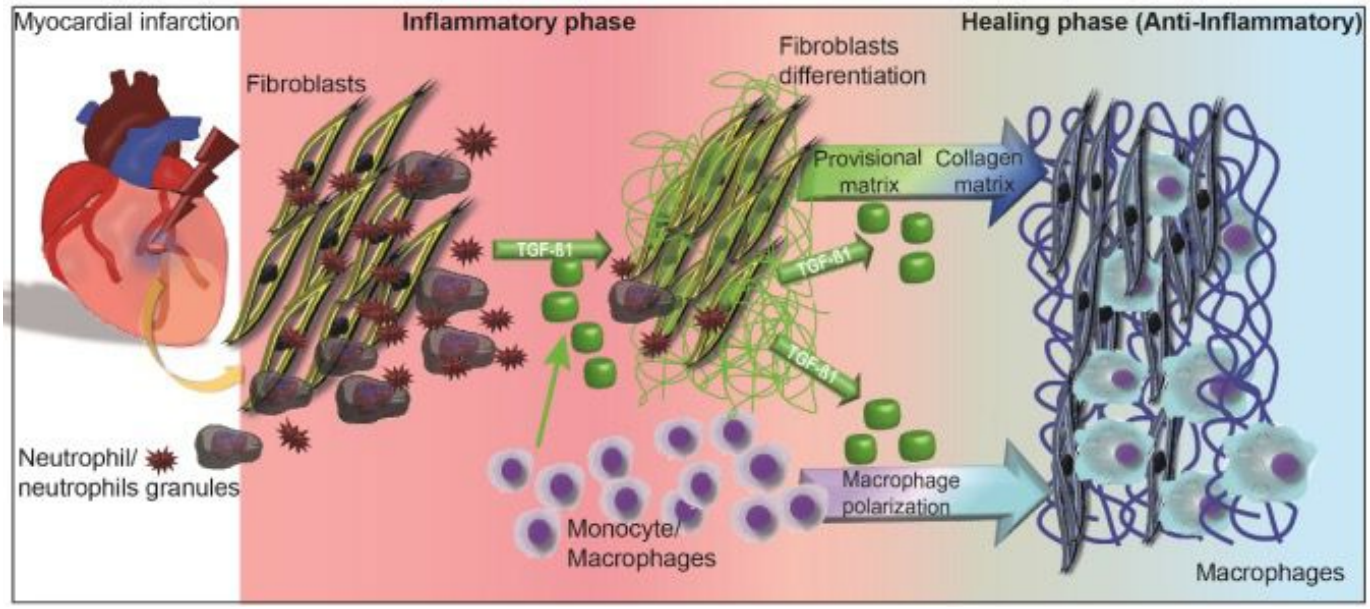

Figure 5. Healing after MI. MI is followed by fibroblasts proliferation. TGF-1 causes fibroblast differentiation, collagen production, and polarization of macrophage. When TGF-1 expression reaches a high level, a negative feedback mechanism is triggered, lowering TGF-1 expression, and finish the mature scar.[15]

resolution during the reparative phase. It also the result of subsequent amplification or a second wave of resurgent immune activation in response to poorly characterized factors. Disturbances in the suppression and resolution of the inflammation may play a role in the development of unfavorable remodelling and heart failure.[14]

The transition between the inflammatory and proliferation phases is decisive. As soon as the necrotic cells and matrix debris are removed, the rapid inhibition of inflammation by TGF- and IL10 is essential for the optimal infarct healing. Along with suppressing cytokines and chemokines of the inflammatory phase, TGF- suppresses the expression of CXCL10 (angiostatic factor) and allows angiogenic factors, such as CXCL12, CXCL1, CXCL2, MIF, and CCL2, to exert their function.[16]

Immune cells are known to interfere with cardiac fibroblasts, which is needed for extracellular matrix synthesis and scar formation.15 By number, cardiac fibroblasts are the most abundant cell type in the healthy heart.[17] Cardiac fibroblasts are stimulated following myocardial infarction. During fibroblast proliferation, an initial provisional extracellular matrix rich in fibrin/fibronectin is produced.[15]

Mechanical stress, the renin-angiotensin-aldosterone system (RAAS), and fibrogenic growth factors are also involved in both reparative and reactive fibrosis. When activated by these factors, the fibroblast proliferates and differentiates into a nonproliferative secretory phenotype, the myofibroblast. Myofibroblast combines characteristics of smooth muscle cells acquired through formation of contractile stress fibers and the expression of a smooth muscle actin, with an extensive endoplasmic reticulum. The myofibroblast regulate extracellular fibrillary collagen types I and III turnover, and autocrine and paracrine factors that simulate their metabolic activity, perpetuating fibrogenesis. The myofibroblast also secretes in excess matricellular proteins, that play an important role in the regulation of fibrosis.[18]

Infarcts are classified according to their size: microscopic (focal necrosis), small (10% of the left ventricle), medium (10% -30% of the left ventricle), or large (>30% of the left ventricle). Infarcts are also classified according to their location (such as anterior, inferior, posterior, lateral, septal, or incorporation of locations).[6] One of the most significant predictors of post-MI ventricular function is infarct size. Larger quantities of ischemic tissue result in more severe dysfunction throughout the whole post-MI healing process. The size of the ischemic region determines the degree of systolic impairment in the acute stage following MI.[17] The left ventricle is made up of approximately 4 billion cardiomyocytes. Late heart failure develops after an acute myocardial infarction when approximately 25% of the left ventricle is involved, and cardiogenic shock occurs when 40% of the myocardium is affected.[4] In another research, infarct size at 3 months after MI was a strong predictor of 1.5-year mortality than LVEF or LV volume.[17]

Savage et al. discovered that systolic wall thickening decreased with the increasing degree of necrosis in a porcine model. Clinically, patients with greater infarcts at the time of admission have lower cardiac output and stroke volume, lower left ventricle stroke work, and higher LV filling pressures. PET and gadolinium-enhanced MR imaging studies used to determine infarct size found increased risk of death or reduced event-free survival 2-3 years after MI in groups with large infarcts.[17]

6. Reperfusion and STEMI

The pathophysiology of myocardial infarction and the time course of irreversible myocardial damage are the guiding concepts for myocardial infarction treatment. The goals of acute myocardial infarction management include minimizing the duration of myocardium exposure to ischemia, rapidly establishing effective reperfusion, preventing recurrent ischemia and re-occlusion, managing arrhythmic and mechanical complications, and modifying underlying atherosclerosis in the long term.[19]

A rapid and early restoration of blood flow in ischemic tissue is critical to ensure cell recovery if the damage is reversible. Despite its obvious usefulness, reperfusion is linked with a number of adverse cellular alterations. 10 Furthermore, reperfusion changes the gross and

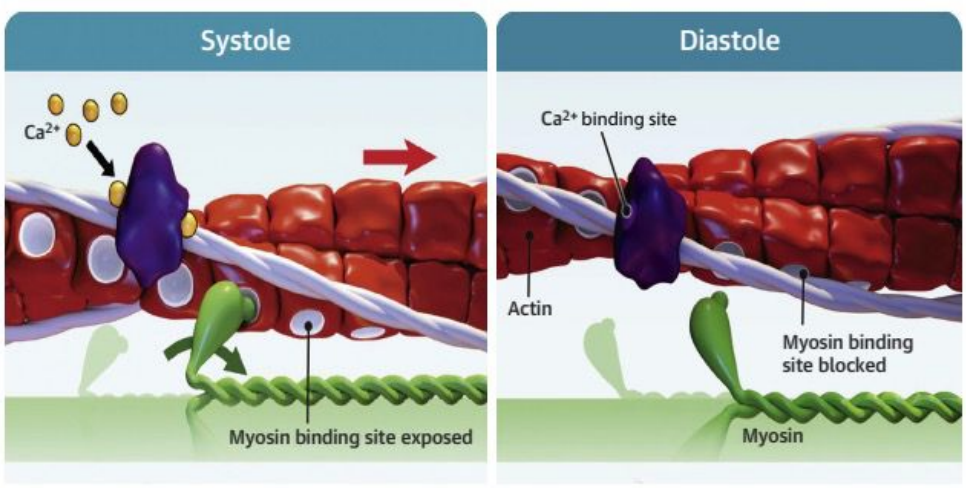

Figure 5. Calcium binds troponin during systole, exposing myosin binding sites on actin filaments and enabling the cross bridges. Active calcium uptake is shielding myosin binding sites on actin from myosin. 23

microscopic appearance of the necrotic zone by generating myocytes with contraction bands and a high number of extravasated erythrocytes.[6]

Lessen the time between ischemic myocardium and reperfusion in STEMI patients is important for salvaging ischemic myocardium, limiting residual damage, lowering the risk of future heart failure, and improving survival. The reperfusion within 60 to 90 minutes after ischemia start results in the most efficient rescue of myocardium. The first 60 minutes of infarction has been known as the "golden hour" because restoring myocardial function is best accomplished during this time, and some patients even experience aborted infarction without evolving electrocardiographic changes and without mechanical deficiency.[19]

Mechanical reperfusion of coronary arteries is the preferred therapy in STEMI because, as compared to fibrinolysis, it improves arterial patency, reduces the risk of reinfarction, lowers the risk of stroke, and improves survival. Stent implantation has been shown to be more effective than balloon angioplasty.[4]

Therapeutic strategies for preventing atherosclerosis complications focus on reducing systemic and local inflammation while also stabilizing the plaque. Statins appear to reduce inflammation, increase collagen in the fibrous cap, and reduce plaque size in addition to lowering lipids, effectively lowering the risk of ischaemic events. Methotrexate and ciclosporin are also used as systemic treatments.[4]

The main pathogenetic factors involved in the initiation and progression of late detrimental cardiac remodeling in patients with acute myocardial infarction after effective reperfusion with PCI are distal embolization, stunning/hibernating myocardium, atherosclerotic progression, inflammation, fibrosis, and impaired cardiac and vascular restoration.[20]

The time it takes for the left ventricle to recover after myocardial infarction is debated. Baron et al. found that global longitudinal strain (GLS), measured by echocardiography, 1 year after myocardial infarction was improved compared to baseline in patients with normal EF. All patients that enrolled were treated according to clinical practice. [21]

7. Cellular mechanism of Diastolic Dysfunction

Calcium homeostasis, which includes calcium release, recapture, and storage, is critical for sustaining excitation–contraction coupling in cardiomyocytes. Ca2+ is mostly found in extracellular and also intracellular organelles such as the sarcoplasmic reticulum and mitochondria. When a cardiac action potential occurs, Ca2+ enters the cell from extracellular through L-type Ca2+ channels (LTCC). The intracellular Ca2+ activates ryanodine receptor 2 (RyR2), so sarcoplasmic reticulum release additional Ca2+.[13]

Before contraction, the concentration of Ca2+ ions in the cytoplasm rises (from approximately 0.1 μM to 1 μM). The troponin C, a contractile apparatus protein, binds Ca2+ ions when the cytoplasmic Ca2+ concentration exceeds 1 μM. Then troponin C changes shape, allowing contact between myosin and actin, sliding of actin filaments between myosin filaments, and cell shortening (contraction).[22]

Ca2+dissociation from myofilament protein stretches myocardial cells.[13] It's the first step in the relaxation process. It starts with the removal of Ca2+ ions from the cytoplasm, which allows Ca2+ to be disconnected from troponin C, actin and myosin to be disconnected, and relaxation to occur. After myocardial contraction, ion transporters that responsible for the reduction of Ca2+ ions from the cytoplasm are sarco-endoplasmatic reticulum calcium ATPase (SERCA), Na+/Ca2+ exchanger (NCX), and plasma membrane calcium ATPase (PMCA).[22]

The primary route of Ca2+ eflux is through the NCX, which is located in the cell membrane. NCX reacts rapidly to intracellular Ca2+ variations depending on Ca2+ level. According to 3Na+ : Ca2+, NCX conducts internal and extracellular ion exchange. The direction of calcium flow is determined by the concentrations of Na+, Ca2+, and membrane potential both within and outside the cell.[13]

After separating myosin and actin, the next step in the relaxation process is to restore the resting length of sarcomeres. Titin, a sarcomere protein, plays a key function in this step. With a molecular mass of 3-4.[2] MDa, it is the largest known protein. In the middle of the sarcomere, titin stretches from Z line to the M line. The titin molecule has two functional parts: rigid, which is made up of immunoglobin-like

components and binds to myosin, and elastic, which is located between the Z disc and the beginning of the myosin and has elastic domains constructed in between rigid Ig elements.[22]

Titin, a massive protein, serves as an elastic spring that recoils during diastole. There are isoforms of the protein that are more (N2BA) or less (N2B) compliant. In HFpEF patients, the percentage of N2B is higher. In HFpEF, restoring forces and elastic recoil are typical because N2B is the stiffer isoform. Protein kinase G phosphorylation of titin results in a more compliant molecule, while protein kinase C phosphorylation and disulfide bond formation results in a stiffer structure.[23]

Ca2+ removal from the cytoplasm is obligated for cardiomyocyte relaxation. It allows Ca2+ to be disconnected from troponin C, actin and myosin to be disconnected, and relaxation to occur sequentially. The rate at which Ca2+ ions are removed from the cytoplasm determines the rate at which they are disconnected from troponin C.[22] In STEMI patients, stimulation of β adrenergic receptors promoting Ca2+ influx by LTCC and also enhancing Ca2+ release by RYR2.[24] The availability of ATP was reduced in STEMI patients. The increase in Ca2+ in the cytoplasm causes an increase in Ca2+ in the mitochondria, which further reduces ATP synthesis.10 We know that the movement of Ca2+ ions to the sarcoplasmic reticulum consumes energy. SERCA consumes about 15% of cardiomyocyte ATP.[22]

Impairment of active relaxation and increased passive stiffness are predominant pathophysiological mechanisms leading to diastolic dysfunction.[25] Excess production and accumulation of extracellular matrix structural proteins, or fibrosis, also impedes ventricular contraction and relaxation, resulting in increased stiffness of the myocardium. Excess collagen deposition and fibrosis have been clearly linked to myocardial stiffness.[18]

8. Outcome of Diastolic Dysfunction post myocardial infarction

In a multivariate study of 2797 patients having primary PCI in the HORIZONS AMI trial, Planer et al. discovered that left ventricular end diastolic pressure (LVEDP) was an independent predictor of poor outcomes. Patients with LVEDP greater than 18 mm Hg (above the median) had a higher risk of death at 30 days and 2 years compared to patients with LVEDP less than 18 mmHg.[26]

Yajima et al investigated long-term outcomes of LV diastolic dysfunction in STEMI patients. Patients were followed up for an average of 10.4 years. The temporal constant of LV relaxation (tau) was estimated from LV pressure waves using a catheter-tipped micromanometer to calculate the LV diastolic function. Tau ≥ 50 msec at 2 weeks after STEMI was shown to be a significant predictor of cardiac events in STEMI patients. In a multivariate analysis, individuals with a longer tau were 4.2 times more likely than those with a shorter tau to have cardiac events (p = 0.0022, 95 percent confidence range, 1.678-11.212).[27]

In another research regarding the predictive relevance of high LVEDP in STEMI patients, the measurement of LVEDP prior to coronary angiography during initial catheterization and prehospital discharge catheterization was conducted. Those with the highest LVEDP had the highest incidence of mortality and heart failure hospitalizations during a three-year median follow-up. The LVEDP reduced slightly from 18 mmHg to 15 mmHg from the first to the prehospital discharge catheterization (p=0.01).28

9. Conclusion

Myocardial infarction with ST segment elevation shows totally occluded coronary artery causing hypoxia of the related myocardium, resulting in the anaerobic metabolism, excess proton intracellular, decrease of PH, ATP depletion, acute immune cells recruitment. Then the inflammatory phase changes to a reparative and proliferative phase with the myofibroblast proliferation. This changes in metabolic process may impair diastolic function. LV diastolic dysfunction in STEMI patients was an independent predictor of poor outcomes. Rapid and early reperfusion is critical to ensure cell recovery.

10. Declarations

10.1. Ethics Approval and Consent to participate
Not applicable.

10.2. Consent for publication
Not applicable.

10.3. Availability of data and materials
Data used in our study were presented in the main text.

10.4. Competing interests
Not applicable.

10.5. Funding source
Not applicable.

10.6. Authors contributions
Idea/concept: IK. Design: IK. Control/supervision: AFR, SW, CT. Data collection/processing: IK. Analysis/interpretation: AFR, SW, CT. Literature review: AFR, SW, CT. Writing the article: IK. Critical review: AFR, SW, CT. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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