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Review Article

The role of colchicine on ventricular remodelling following myocardial infarction and ischemia-reperfusion injury: article review

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ABSTRACT

Acute myocardial infarction (AMI) is a major cause of cardiac dysfunction, arrhythmias, and a poor prognosis. Even though new technologies have been developed to aid in opening the culprit coronary artery and correcting ischemia-related stenosis by percutaneous coronary intervention (PCI), the ventricular remodelling that induces cardiac failure as a consequence of AMI remains unchanged. Colchicine, a versatile anti-inflammatory medication, has been documented in mitigating cardiac remodelling and enhancing cardiac function following AMI. This article provides an in-depth review of the processes by which colchicine affects ventricular remodeling after AMI, highlighting the potential role of inflammation in the pathogenesis and progression of ventricular dysfunction.

1. Introduction

Even though new technologies have been developed to aid in opening the culprit coronary artery and correcting ischemia-related stenosis by percutaneous coronary intervention (PCI), the ventricular remodelling that induces cardiac failure as a consequence of acute myocardial infarction (AMI) remains unchanged. Ventricular remodelling following myocardial infarction (MI) is observed in over 30% of individuals who have experienced an anterior MI, whereas the occurrence of such remodelling is roughly 17% in patients with non-anterior infarcts.[1] The inflammatory response following AMI is a contributing factor to cardiac remodelling, exacerbating the detrimental effects of ischemia-reperfusion injuries. This response ultimately leads to an enlargement of the infarcted area and a worsened prognosis for the patient.[2]

The inflammatory state serves as a significant indicator of worse outcomes following AMI. Hence, it may be concluded that inflammation holds significant potential as a viable treatment target for individuals diagnosed with AMI. A number of anti-inflammatory medicines exhibit potential as viable choices, however their investigation within this particular context has been limited thus far.[3] The efficacy of colchicine, a versatile anti-inflammatory medication, has been documented in mitigating cardiac remodelling and enhancing cardiac function following AMI. This chemical exhibits diverse anti-inflammatory properties by inhibiting the phenomenon of neutrophil chemo-attraction, the intricate network of inflammasomes, and the release of pro-inflammatory cytokines.[4] This article provides an in-depth review of the processes by which colchicine affects ventricular remodelling following myocardial infarction.

2. Discussion

Myocardial Infarction

Pathology of Myocardial Infarction

From a pathological standpoint, MI is characterised as the demise of cardiomyocytes resulting from an ischemia injury that caused by imbalance between demand and supply of oxygen to the myocardium. The utilisation of this concept within the clinical setting presents difficulties due to the reliance on the clinical criterion specificity and sensitivity, electrocardiographic (ECG) data, imaging investigations, and biomarkers for the identification of MI.[5] MI is mostly attributed to a reduction or cessation of blood supply to a specific region of the heart, resulting in the death of cardiac muscle tissue.[6] This phenomenon typically occurs as a consequence of a thrombus formation within the epicardial artery responsible for supplying blood to the specific region of the cardiac muscle as well defined as MI type I caused by atherosclerotic disease.[7] Based on ECG and its own pathophysiology, MI classified into Non-ST Elevation Myocardial Infarction (NSTEMI) and ST-elevation Myocardial Infarction (STEMI).[8]

Basic Pathophysiological Effects of Myocardial Infarction

Cardiomyocytes have ample energy reserves to sustain contractility regarding a brief period in terms of overall ischemia. Systolic dysfunction occurs rapidly, with contractile force being Cleaned down and ceasing after the sixty-second ischemia.[5] The myocardial dysfunction varied in terms of its severity, ranging from a quick and completely reversible stage known as myocardial stunning, to an irreversible necrotic stage referred to as myocardial infarction.[9]

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In reversible stage, less tissue oxygen drove anaerobic respiration, which lowered ATP synthesis and pH through lactate accumulation within minutes of ischemia onset. In addition, early electron transport chain reactive oxygen species (ROS) may oxidize contractile proteins. Full healing is conceivable if oxygen balance restored within 15-20 min. For longer periods, ROS, acidosis, and decreased ATP levels degrade contractile performance and deform cardiomyocytes, resulting in systolic dysfunction and delayed myocardial recovery as seen in myocardial stunning stage. Furthermore in infarction stage, high ROS production in prolonged untreated ischemia (>30 min) increases intracellular calcium, causing permanent cardiac necrosis (Infarction) and acute inflammatory response.[9]

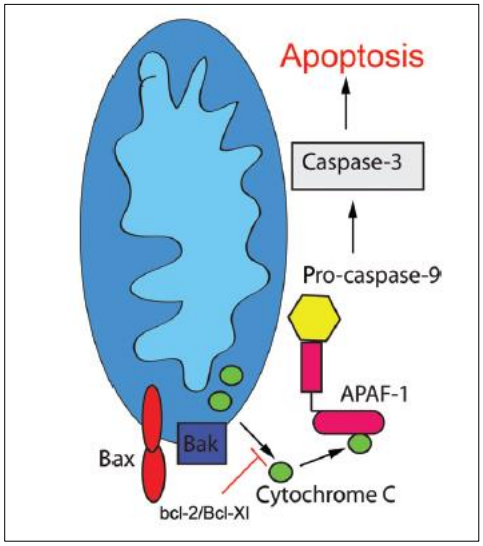

Figure 1. In the ischemic heart, mitochondrial dysfunction is crucial for cardiomyocyte death. Through Bcl-2 family members, proapoptotic stimuli membrane permeabilization of the outer mitochondria. Afterward, mitochondrial apoptogens such cytochrome-c enter the cytoplasm, triggering apoptosis. Adaptor protein apoptotic protease activating factor 1 (Apaf-1) oligomerizes and recruits procaspase-9 when cytochrome-c binds to it. Caspase-9 activates downstream caspases, leading to apoptosis by cleaving cell proteins.[10]

Molecular Mechanisms of Cell Death in the Myocardial Infarction

There are two proposed mechanisms by which cardiac cells terminate their lives: apoptosis, which is a programmed process characterized by phagocyte-mediated removal of the cells, and necrosis, which is an unregulated process involving cell membrane loss and contraction. Necrosis emits danger signals that induce substantial inflammation, whereas apoptosis eliminates deceased cells without inducing inflammation. Through mitochondrial signaling and death ligand binding to cell surface death receptors, infarcted hearts undergo apoptosis. The infarcted myocardium's cardiomyocyte necrosis and apoptosis are linked to ischemia-mediated mitochondrial dysfunction. Apoptosis of cardiomyocytes requires that B-cell lymphoma 2 (Bcl-2) family members permeabilize the outer mitochondrial membrane (OMM) (Fig. 1). Necrosis, as opposed to apoptosis, is characterized by the emergence of the mitochondrial permeability transition pore (mPTP) within the inner mitochondrial membrane. Water enters the mitochondrial matrix when mPTP is opened, resulting in severe edema and cardiomyocyte destruction. OMM rupture induced by unregulated mitochondrial water input liberates apoptogens and triggers caspase activation.[10]

Reperfusion as The Treatment of Myocardial Infarction and Related Injury

Ischemic individuals with a STEMI diagnosis and symptoms lasting ≤12 hours should undergo reperfusion treatment. Use PPCI instead of fibrinolysis if diagnosis to PCI time is <120 min with Class 1A recommendation.[11] Due to the efficacy of reperfusion techniques such as PPCI and thrombolysis, the mortality rate associated with acute myocardial infarction has ended. In STEMI patients undergoing PPCI, the door-to-balloon time has decreased, but in-hospital mortality has remained unchanged. [12] Infarct size within one month of PPCI forecast the occurrence of all-cause mortality and hospitalization related to heart failure. at one year, according to a recent patient-level meta-analysis. This supports the use of infarct size as a meaningful surrogate endpoint in therapeutic studies.[13]

While early and thorough reperfusion is crucial for reducing infarct size and ventricular remodeling, it also causes irreparable damage to the myocardium and coronary circulation, contributing to the final infarct size (Fig.2).[14] Most cardiomyocytes undergo necrosis during ischemia, although reperfusion may trigger potent proapoptotic mechanisms, increased apoptotic cardiomyocyte mortality and this called myocardial ischaemia/reperfusion injury.[10] At later times, biomechanical stress and infarcted area proinflammatory pathways may cause A subsequent surge in cardiomyocyte demise that is less intense than acute ischemia loss. In contrast to achieve patency of the epicardial infarcted artery, preventing and treating lethal reperfusion injury and coronary microvascular dysfunction remain the final boundary of reperfusion therapy.[12]

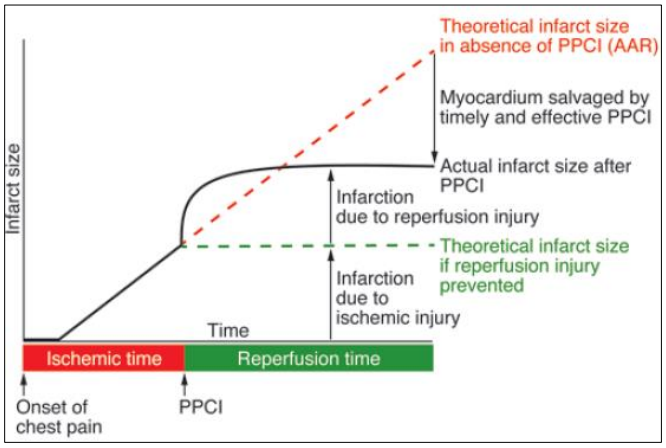

Figure 2. This figure shows how acute myocardial ischemia injury and reperfusion injury affect STEMI patients' ultimate MI size up to 24 hours after PPCI.[14]

3. Myocardial Ischemia/Reperfusion Injury

Patophysiology of Myocardial Ischaemia/Reperfusion Injury

Figure 3 illustrates the mechanisms that contribute to myocardial reperfusion injury in the coronary vascular compartment and cardiomyocytes.[15] Over time, the notion that reperfusion of acutely ischemic myocardium can result in cardiomyocyte mortality has become more difficult to accept. Myocardial stunning, reperfusion-induced arrhythmias, microvascular obstruction, and fatal myocardial reperfusion injury are the four recognized types of myocardial reperfusion injury, with the first two being reversible and the last two being irreversible.[14]

Biphasic ischemia/reperfusion (I/R) injury is a concept that has been established with certainty. Reperfusion restores the substances required for ATP and oxygen production in the cardiomyocyte compartment, resulting in pH normalization and the elimination of catabolic waste products. The presence of these hormones is vital for the maintenance of cardiac tissue. However, these same factors can unexpectedly exacerbate cell damage in cardiomyocytes that have suffered a severe lack of blood flow, resulting in a transition from reversible to irreversible damage. Reperfusion rapidly normalizes extracellular pH, creating a significant plasma membrane H^+ gradient. Another enormous flow of Na^+ inside the cell allows surplus H^+ ions to be expelled by the Na^+/H^+ exchanger.[16]

When there is a spike in the level of sodium inside the cell, a protein complex known as the sodium-calcium exchanger (NCX) will export sodium ions and bring in calcium ions. After 30–60 minutes of physiological calcium reestablishment in the cytoplasm, calcium-

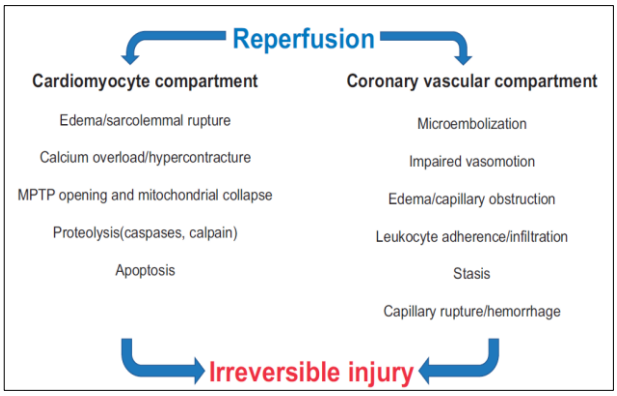

Figure 3. Interacting mechanisms within the coronary vascular compartment and cardiomyocytes that contribute to irreversible ischemia/reperfusion injury.[15]

dependent lipases and proteases become active, cell hyper-contraction takes place, and the mitochondrial permeability transition pore (mPTP) opens. All of these events take place simultaneously. An excessive conductance opening leads to mitochondrial depolarization, swelling, and an excessive release of cytochrome C and Ca^{2+}, all of which activate the intrinsic pathway leading to apoptosis and necrosis.[16]

Reperfusion damage in the coronary circulation leads to microvascular dysfunction in the coronary vascular compartment. This dysfunction is brought on by an increase in capillary permeability, which in turn leads to edema. Because of this insult, atherosclerotic debris, platelets, leukocytes, and erythrocyte aggregates are formed, all of which have the potential to produce coronary microembolization. In addition, the injury causes damage to the endothelium cells as well as the smooth muscle cells, which prevents the blood vessels from being able to contract and relax as they normally would. In addition, it leads to the breakdown of capillaries as well as bleeding. It is possible that the formation of reactive oxygen species, often known as ROS, plays an important part in the pathophysiological mechanism that underlies myocardial and coronary microvascular reperfusion injury.[15]

Inflammatory Pathway of Myocardial Ischemia/Reperfusion Injury

The abrupt reintroduction of oxygen that occurs when blood flow is restored might make tissue damage worse. This results in the production of additional reactive oxygen species (ROS) and the activation of the complement system (Fig. 4). The damaged cardiac parenchymal cells, the extracellular matrix that has been degraded, and the chemicals that have been created all act as danger signals. These danger signals are known as danger associated molecular patterns, or DAMPs for short. Attachment of DAMPs to pattern recognition receptors (PRRs) on parenchymal cells (such as cardiac fibroblasts and resident macrophages) and on invading leukocytes causes the innate immune system to release a cascade of inflammatory mediators.[17]

The pattern recognition receptors (PRRs) include cell-surface receptors for advanced glycation end products, toll-like receptors/IL-1 receptors that are connected to the cell membrane, and cytosolic nucleotide-binding oligomerization domain-like receptors (NLRs). All of these receptors are found in the cytosol. The activation of the mitogen-activated protein kinases and NF-kB pathways, in addition to the NLR family pyrin domain containing protein 3 (NLRP3) inflammasome, is the conclusion of the PRRs' downstream signaling. The following recruitment of leukocytes not only amplifies the inflammatory response, but it also makes it easier to remove dying cells and facilitates the breakdown of tissue, which contributes to the progression toward resolution of inflammation.[17]

Pathological Alterations of Ventricular Remodelling After MI and I/R Injury

Cardiac remodeling is an intricate process that includes both the immediate events that occur within 90 minutes of a STEMI (so as reperfused STEMI), as well as the long-term events that occur in the months or even years following the infarction (Fig. 5). During the earliest stage of MI, the restructuring of the heart is influenced by the enlargement of the damaged area and can be observed within a few hours to days after the acute event. Myocardial necrosis causes an increase in inflammatory cells and resulting in the breakdown of the collagen structure. This leads to changes in the form of the ventricles, thinning of specific regions, and expansion of the myocardium in the areas affected by the infarction.[18]

During the subsequent weeks to months, the healthy heart muscle continues to face several pathological occurrences. These include the activation of enzymes that break down proteins and an increased production of signaling molecules, particularly those that can trigger the death of heart muscle cells and promote the release of inflammatory substances. The last stage encompasses responsive enlargement of heart muscle cells, excessive growth of connective tissue between cells, and expansion of the left ventricle.[18]

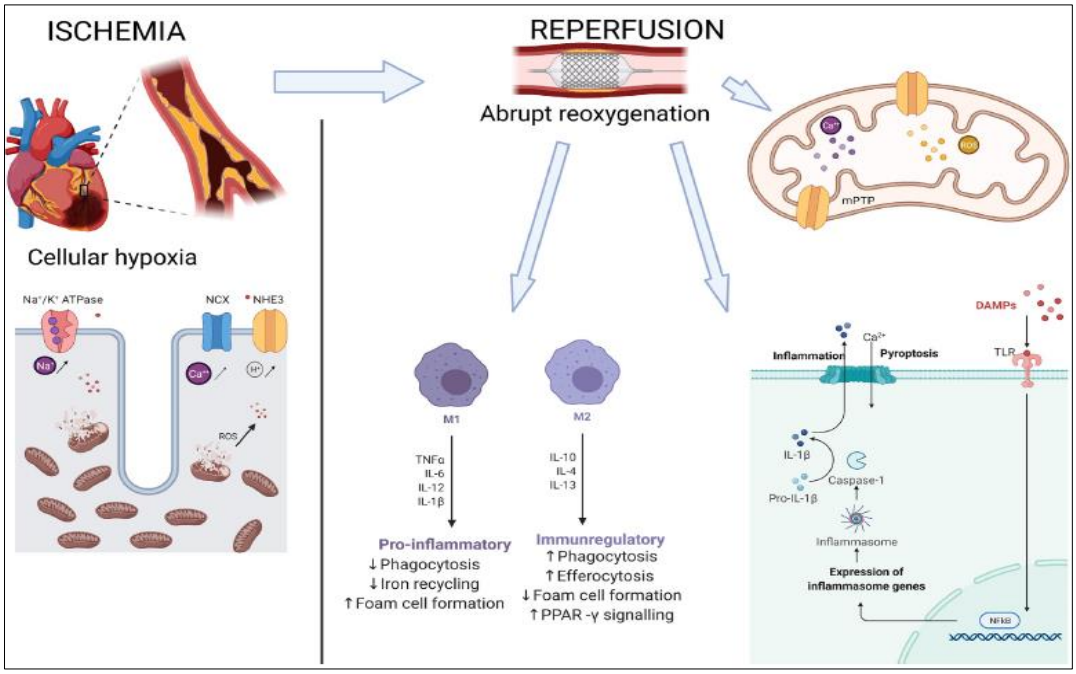

Figure 4. Schematic overview of I/R injury.[17]

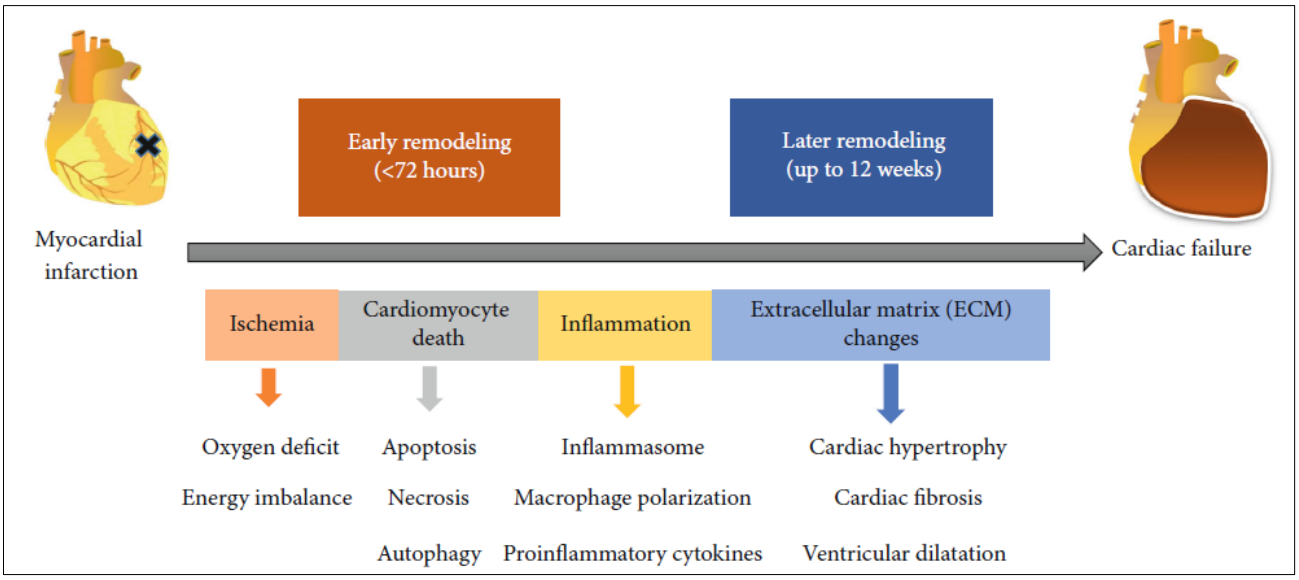

Figure 5. The stages and primary pathological alterations in cardiac remodeling following a myocardial infarction.[18]

4. Ventricular Remodelling Following Myocardial Infarction and Ischemia-Reperfusion Injury

Mechanical Patophysiology of Post-MI Myocardial Remodelling

Changing left ventricular geometry and wall stress are the main mechanical mechanisms affecting ventricular remodeling following MI. Infarcted segments stretch early in unfavorable remodeling due to a lack of counterweight to the typically contracting myocardium. Thus, increasing wall tension from this level thins the infarcted wall and expands the MI in nearby regions. LV volume and pressure overload on non-infarcted zones are increased by stretched and dilated infarcted tissue. In late remodeling, healthy cardiomyocytes stretch and enlarge to maintain a normal stroke volume with fewer adequately functioning myocardial segments under increased stress. Finally, overstretching loss of the compensatory Frank–Starling mechanism causes LV dilatation. A vicious loop occurs when LV dilatation increases WS, which increases chamber dilation and wall thinning.[19+]

Early Cellular Changes in Post-MI Ventricular Remodelling

During this phase, stimulation of TLR by DAMPs activates NF-kB, which has the ability to set off a chain reaction that involves prointerleukine-1b (pro IL-1b) and prointerleukine-18 (pro IL-18). Inflammasomes and caspase-1 can both be activated by DAMPs, and these two enzymes are responsible for the maturation of pro IL-18 and pro IL-1b into their active forms. Because of this chain of events, neutrophils and other inflammatory cells migrate to the infarct zone, which contains a high concentration of pro-inflammatory cytokines such as IL-18, IL-1b, tumor necrosis factor a (TNF-a), and particular interferons.[20]

The initiation of scar formation occurs within the infarct region, where neutrophils are substituted by anti-inflammatory macrophages of the M2 phenotype. Additionally, lymphocytes, natural killer cells, dendritic cells, and myofibroblasts play crucial roles in this process. Furthermore, the levels of anti-inflammatory cytokines, including interleukin 10 (IL-10) and transforming growth factor b (TGF-b), progressively rise during scar formation. The key mediator of postinfarction healing is transforming growth factor β. This is achieved by augmenting the matrix via activation of the Smad3 signaling pathway.[20]

In addition, TGFb/Smad cascade mediates profibrotic effects of hormones like aldosterone and angiotensine-2. Notably, TGF-b, platelet-derived growth factor, and neutrophils cause myofibroblasts to form from fibroblasts, which do not exist in normal myocardium. New myofibroblasts serve a crucial role in infarct repair by promoting collagen production and inducing replacement and reactive fibrosis in the infarct tissue and remote myocardial segments. In some cases, aberrant healing responses may lead to adverse myocardial remodelling (AMR) development post-AMI.[20]

Late Cellular Changes in Post-MI Ventricular Remodelling

Following the process of infarct recovery, it is possible for cardiac tissue to induce systemic inflammation as a result of myocardial wall stress, encompassing myocardial strain and hemodynamic load. This stress triggers the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-a), interleukin-18 (IL-18), interleukin-6 (IL-6), and interleukin-1 beta (IL-1b). In recent studies, a correlation has been established between the IL-23/IL-17A axis and the emergence of late antibody-mediated rejection (AMR). Specifically, the involvement of gamma-delta T (gdT) cells and other associated cell types has been identified in this process.[20]

It should be noted that infiltration of gdT cells and expression of IL-17A occur at a later stage following infarct healing and are not associated with acute inflammation during the early post-acute myocardial infarction (AMI) period. In contrast, IL-17A stimulates the expression of IL-1β, TNF-α, IL-6, and particular matrix metalloproteinases (MMPs) in macrophages. Additionally, it has significant apoptotic and profibrotic effects on distant myocardial areas, which manifest at a later stage. Cardiomyocyte apoptosis is a prominent indicator of late antibody-mediated rejection (AMR) and is initiated by the activation of the p38 MAPK-p53-Bax signaling pathway and the intrinsic apoptotic pathway involving the endoplasmic reticulum and mitochondria. The activation of fibroblasts, upregulation of fibrogenic genes, and overexpression of matrix metalloproteinases (MMPs) and interleukin-6 (IL-6) can be attributed to the direct action of IL-17A, potentially leading to the development of profibrotic conditions.[20]

Extracellular Matrix Changes and Neurohormonal Regulation

The extracellular matrix (ECM) forms a scaffold around cardiac myocytes to maintain LV structure and geometry. A complicated interaction between fibroblasts, collagen, MMPs, and cell surface adhesion molecules occurs in the ECM. Through the balance of MMP and their inhibitors (TIMPs), unfavorable cardiac remodeling actively turns over the ECM. MMPs and TIMPs are regulated regulated at transcriptional and translational levels by several transcription factors and enzymes, including as the NF-κB and JAK-STAT pathways. Importantly, neurohoromonal activity, particularly renin-angiotensin aldosterone system (RAAS) activation, may regulate these pathways.[21]

Neurohormones regulate unfavorable cardiac remodeling and can be targeted pharmacologically to prevent and reverse it.

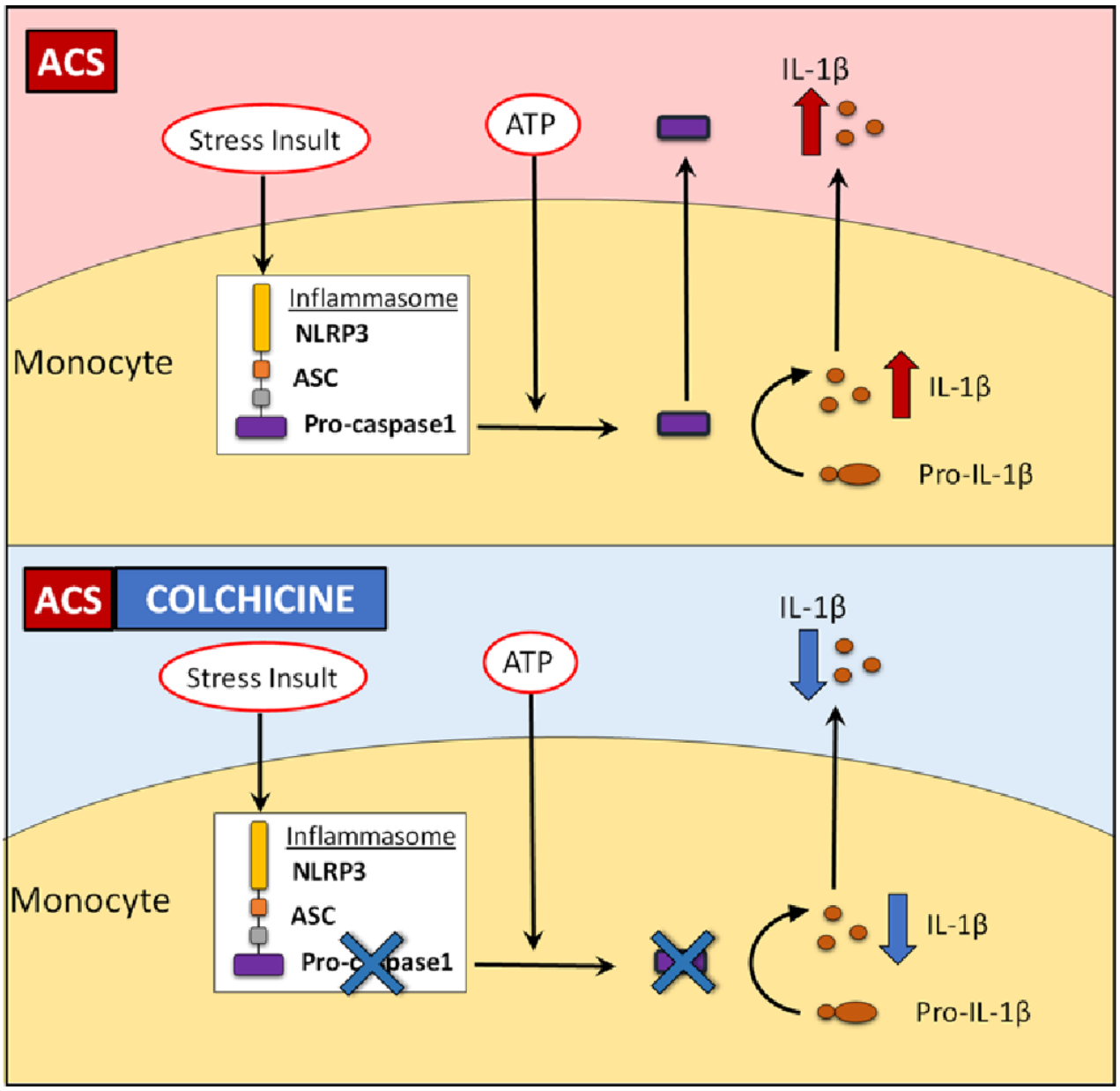

Figure 6. Effect of short-term colchicine on caspase-1 expression and IL-1β production in monocytes from ACS patients.[24]

The sympathetic nervous system (SNS) and RAAS are key cardioregulatory hormonal cascades in LV remodeling. The SNS boosts heart rate and stroke volume by releasing β-adrenergic tone. In acute decompensation, these methods may be compensatory, but prolonged sympathetic activity can damage the LV. In addition, persistent catecholamine activity may impair heart function, promote fibrosis, and cause oxidative damage. Chronic SNS stimulation promotes RAAS activation, which mediates angiotensin II's side effects. Increased angiotensin II expression may cause much of RAAS's negative cardiac remodeling. Angiotensin II directly cytotoxically affects cardiac myocytes, accelerating apoptosis and cell hypertrophy.[21]

Post-Infarction Cardiac Remodelling Therapeutical Intervention

Cardiac remodelling has a substantial contribution to the pathogenesis and advancement of ventricular dysfunction, arrhythmias, and unfavourable prognosis. Hence, the mitigation of unfavourable cardiac remodelling represents a crucial objective in the therapeutic approach to addressing AMI. Pharmacological treatments are developed by targeting the fundamental pathophysiological mechanisms.[18] Given the significant involvement of inflammation in ventricular remodelling after a myocardial infarction, many cytokines could serve as potential targets for therapeutic intervention in regulating myocardial inflammation. Multiple studies have demonstrated that blocking NLPR3, a large molecule responsible for controlling the activation of IL-1 and IL-18, helps maintain the normal pumping function of the heart after both ischemia and non-ischemic injuries in living organisms.[19]

5. The Role of Colchicine

History of Colchicine

The botanical alkaloid known as colchicine, derived from the flower Colchicum autumnale, was first recorded as a therapeutic plant in the Ebers papyrus of ancient Egypt in 1550 BC. Its reported use was primarily for the management of pain and swelling. The molecular structure of colchicine, scientifically known as N-[(7S)-5,6,7,9-tetrahydro-1,2,3,10-tetramethoxy-9-oxobenzo(a)heptalen-7-yl)acetamide, consists of three interconnected rings.[22] The active compound known as colchicine was discovered during the early 19th century by French chemists Pierre-Joseph Pelletier and Joseph Bienaime´ Caventou. It continues to be utilized in its refined form as a natural product in contemporary times. The term 'colchicine' is etymologically linked to the historical and mythical realm of Colchis, where Jason embarked on a quest to retrieve the Golden Fleece and where C. autumnale vegetation was abundant.[23]

Pharmacology of Colchicine

The jejunum and ileum absorb colchicine. Peak serum concentrations are normally obtained after 0.5–3 h of oral treatment and drop over the next 2 h, but enterohepatic recycling raises them. Bioavailability is variable (mean 45%). Leucocytes, especially neutrophils, express little P-glycoprotein, hence colchicine is greatly concentrated in them. Intracellular neutrophil counts peak within 48 h after a single 1mg oral dose in healthy people, hence its acute biological effects take 24–48 h to occur. The elimination half-life of colchicine is 27–31 h. Its biological effects on leucocytes diminish within 48 h after withdrawal. Ten to thirty percent of the medication is protein-bound. The kidneys (20–40%) and bile (60–80%) excrete colchicine, which is largely metabolized in the liver via de-acetylation with a half-life of 12–30min. These two routes may decrease medication clearance, increasing drug accumulating risk.[23]

Acting Mechanism of Colchicine as Anti-Inflammatory and Anti-Fibrotic Agent

The pleiotropic impact of this alkaloid is associated with its ability to attach to tubulins and disrupt the polymerization of microtubules. Colchicine attaches to soluble tubulins and, depending on the dosage, can either hinder the elongation of microtubules or, at larger dosages, trigger the breakdown of microtubules. Colchicine has pleiotropic effects, including modulation of the immune system and anti-inflammatory capabilities.[2]

Colchicine exerts its effects through various mechanisms; however, at its core, it disrupts microtubule depolymerization by binding to tubulin; this, in turn, impedes mitosis, exocytosis, inflammatory cell migration, and phagocytosis. Colchicine additionally hinders the activation of the NLRP3 inflammasome by cholesterol crystals and restricts the synthesis of IL-1β, IL-18, as well as IL-6 and CRP that are produced downstream as seen in fig.6.[24] Additionally, evidence suggests that colchicine exhibits pharmacodynamic benefits that extend beyond its maximal plasma concentration duration. This suggests that leucocyte accumulation increases, leucocyte activation decreases, and leucocyte adherence to vascular endothelium is reduced.[25]

Colchicine modulates inflammatory responses via multiple pathways, which encompass impeding the adhesion of neutrophils to the vascular endothelium, inhibiting the production of interleukin-1 by activated neutrophils, and downregulating tumor necrosis factor-α receptors in macrophages and endothelial cells. It is probable that these effects are facilitated through the regulation of surface expression of neutrophil L-selectin and endothelial E-selectin.[26]

Colchicine, functioning as an anti-fibrotic agent, suppresses the expression of VEGF and activation of TGF-β1 in canine models. According to a published study, colchicine inhibits the penetration of neutrophils into the intimal layer and reduces collagen production and fibroblast proliferation, thereby exhibiting anti-fibrotic properties. An additional investigation documented a sterile pericarditis model in rats that was administered colchicine. Colchicine inhibited the expression of proinflammatory markers and fibrosis-related genes, including collagen-1, collagen-3, and α-SMA, as well as IL-6 induced by IL-1β.[27]

Role of Colchicine in Myocardial Infarction and Cardiac Remodelling in Preclinical Models

The inflammatory effects of colchicine have garnered significant interest in the context of acute myocardial infarction (AMI). Numerous animal experiments have been conducted to assess the potential cardioprotective properties of administering low dosages of colchicine. [2] In 2007, Saji et al., demonstrate the inhibitory effect of colchicine in myocardial apoptosis and microtubule polymerization in rats both in vivo and in vitro by supressing caspase-3. This findings proved the potential use of colchicine in preventing the progression of heart failure.[28] Another study on animal subjects demonstrated that colchicine has the potential to impede the advancement of ventricular hypertrophy and have an anti-fibrotic impact. This is achieved by the restructuring of the microtubule cytoskeleton and/or by directly reducing inflammation.[29]

Another recent animal study has likewise focused on the cardioprotective role of colchicine. The administration of colchicine prior to reperfusion demonstrated a notable reduction in inflammation during the initial reperfusion phase in a rat model of reperfused acute myocardial infarction (AMI). The positive impacts of colchicine were shown to be linked with an elevated systemic interleukin-10 (IL-10) concentration and a reduced cardiac transforming growth factor-b level. Additionally, the expression of caspase-1 and pro-IL-18 messenger RNA was found to be reduced by colchicine.[30]

Moreover, 24 hours after ischaemia-reperfusion, a solitary administration of intravenous colchicine (0.4 mg/kg) during ischaemia resulted in decreased infarct size and circulating T troponin levels, suggesting a reduction in myocardial damage. Eight weeks following myocardial infarction, colchicine augments the aortic velocity time-integral, which serves as an indicator of cardiac output, in conjunction with its immediate cardioprotective effects.[31] Colchicine decreased adverse cardiac remodeling, the development of heart failure, and survival following recovery from myocardial infarction following permanent left anterior descending coronary artery occlusion by decreasing acute inflammation and NLRP3 inflammasome activation.[32]

Role of Colchicine in Myocardial Infarction and Cardiac Remodelling in Clinical Practice

Emerging data from the literature is beginning to shed light on the potential impact of colchicine in patients with acute myocardial infarction (AMI), building upon the promising findings observed in fundamental science research. Deftereos et al.'s prospective randomized trial included 151 STEMI patients, 77 of whom received colchicine. This trial administered colchicine in the catheterization laboratory for five days prior to reperfusion (2 mg preload dose). Colchicine dramatically diminished infarct size via cardiac magnetic resonance imaging and reduction of the area under the creatine kinase curve. Inflammatory markers neutrophil count and CRP decreased along with infarct size.[26]

30 days after myocardial infarction, the "Low-Dose Colchicine after Myocardial Infarction" (LoDoCo-MI) study compared the effects of 1 month of low-dose colchicine (0.5 mg daily) versus placebo on residual inflammation as measured by CRP in 237 patients. Notwithstanding a general downward trend in CRP levels within the colchicine group, there was no significant difference in CRP concentrations. The adverse outcomes observed may indicate that prompt administration of the medication would be advantageous in order to maximize its efficacy and reduce reperfusion damage associated with inflammation.[33] After AMI, 4745 patients received colchicine (0.5 mg per day) or placebo in the multinational randomised experiment "Colchicine Cardiovascular Outcomes Trial" (COLCOT). Cardiovascular mortality, resuscitated cardiac arrest, acute myocardial infarction, stroke, or angina hospitalization needing coronary revascularization were the primary endpoints. Colchicine reduced cardiovascular ischemia episodes in the 30 days after an AMI in this trial.[34]

The objective of the next study is to evaluate the effects of colchicine on ventricular remodeling. Patients currently receiving PPCI who have STEMI are being enrolled in the "Colchicine for Left Ventricular Remodeling Treatment in Acute Myocardial Infarction" (COVERT-MI) randomized trial. The anticipated participant pool comprises 194 individuals who will be assigned at random to either a placebo or colchicine, with a loading dose of 2 mg administered during revascularization, followed by a daily dose of 0.5 mg for a period of 5 days. The result was oral administration of high-dose colchicine at the time of reperfusion and for 5 days did not reduce IS assessed by cardiac magnetic resonance imaging.[2] In the recent guidelines of ACS 2023, low-dose colchicine (0.5 mg once a day) may be considered as a long term medication, particularly if other risk factors are insufficiently controlled or if recurrent cardiovascular disease events occur under optimal therapy with the recommendation class of IIb A and level of evidence A.[11]

6. Conclusion

The role of inflammation in the pathogenesis of myocardial infarction and ischemia-reperfusion damage is critical. Adverse ventricular remodeling may develop following a myocardial infarction, whether reperfused or not, and the unfavorable impact will be prolonged as the inflammations continue. Colchicine has been shown to help with myocardial infarction and reperfusion injury by inhibiting the inflammatory pathway.

7. Declaration

7.1 Ethics Approval and Consent to participate
Not applicable.

7.2. Consent for publication
Not applicable.

7.3 Availibility of data and materials
Data used in our study were presented in the main text.

7.4 Competing interests
Not applicable.

7.5 Funding Source
Not applicable.

7.6 Authors contributions
Idea/concept: FC. Design: FC. Control/supervision: IP. Data collection/processing: FC, IP. Analysis/interpretation: FC, IP. Literature review: FC. Writing the article: FC. Critical review: IP. All authors have critically reviewed and approved the final draft and are possible for the content and similarity index of the manuscript.

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