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Cardiac Remodeling: Pathophysiology And Current Management Strategies

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INTRODUCTION

Although the term "cardiac remodeling response" refers to any change in the structure and function of the heart, there are two distinct types of ventricular remodeling: pathological and physiological. (1)

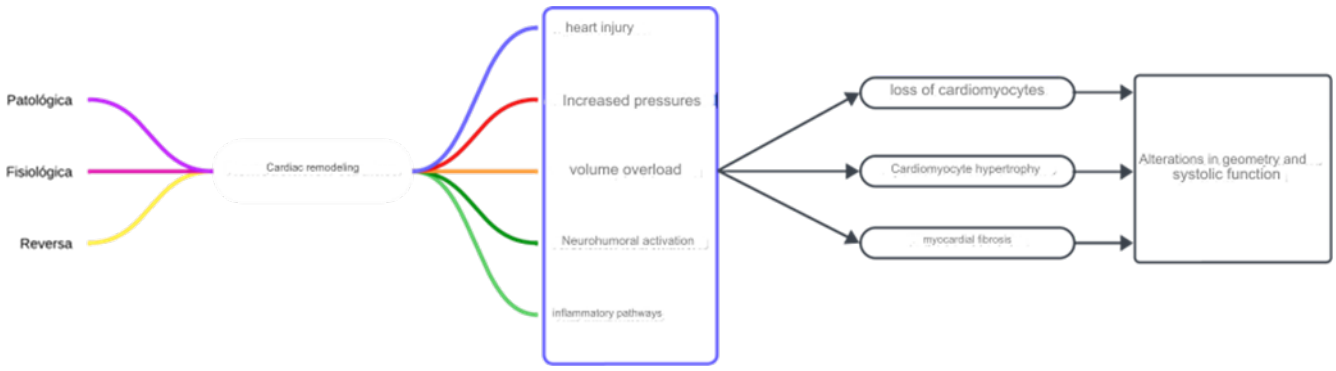
Physiologic hypertrophy, a term for enlargement of the heart in response to growth, exercise, and pregnancy, is related to preservation of normal cardiac function (2). Physiological remodeling of the heart is defined as a well-regulated and coordinated series of advantageous modifications that lead to reduced cardiac wall stress, increased pumping efficiency, and increased vascularization (3). Molecularly speaking, physiological cardiac remodeling is related to well-established signaling pathways such as growth hormone, insulin, vascular endothelial growth factor B (VEGF-B), insulin-like growth factor 1 (IGF1), and the thyroid hormone triiodothyronine (T3). These pathways efficiently regulate cardiac myocyte contractility, sarcomere remodeling, cell survival, metabolic and mitochondrial adaptations, electrical remodeling and angiogenesis, B-type natriuretic peptide (BNP), myosin β-heavy chain (β-MHC), and sarcoendoplasmic reticulum Ca 2+ - ATPase (SERCA2α) (4).

Conversely, when a non-physiological condition or cardiac insult is present, cardiac remodeling mechanisms are triggered to reduce ventricular wall stress and temporarily maintain cardiac pump performance resulting in altered cardiac function and structure, gradually leading to a catastrophic spiral of maladaptive changes leading to heart failure and increased risk of mortality. (5).

The heart often undergoes concentric hypertrophy in pressure overload disorders such as aortic stenosis or hypertension. Cardiomyocytes in these conditions generally thicken more than they elongate, resulting in the formation of a parallel set of sarcomeres, which reduces ventricular wall stress and thickens the free wall and septum (6). The reduction in the number of cardiomyocytes and reorganization of the remaining cardiomyocytes in response to increased workload in volume overload diseases such as myocardial infarction or dilated cardiomyopathy causes eccentric hypertrophy with preferential elongation of cardiomyocytes, which in turn causes serial addition of sarcomeres to accommodate the increased ventricular volumes, and subsequent ventricular dilation (7,8).

Gene transcription, protein synthesis and function, metabolism, and cardiomyocyte survival are affected by these hypertrophic responses, even if they first arise as an adaptive response to decrease wall stress and oxygen consumption. Over time, these modifications also affect interactions between cells and the extracellular matrix (ECM), resulting in fibrosis and angiogenesis (9).

The pathophysiological stimulus leading to pathological cardiac remodeling may vary between cardiac insult, pressure overload, volume overload, neuro humoral activation and activation of inflammatory pathways resulting in cardiomyocyte loss, myocardial hypertrophy and fibrosis resulting in geometric structural changes and consequent alteration of ventricular function that may ultimately trigger heart failure. (10)



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Reverse or reverse remodeling is associated with increased cardiac function and improved prognosis when the geometry and/or function of the left ventricle return to more closely resemble the normal anatomy of the heart. Cardiac recovery or remission refers to the state in which the structure and/or function of the heart have completely returned to normal. However, remodeling is a dynamic process. For example, with the onset of heart failure, a patient may have unfavorable remodeling, followed by reverse remodeling with guideline-directed drug therapy. When guideline-specified medical therapy is discontinued or heart failure worsens, adverse remodeling may recur (11,12).

It is important to emphasize that reverse remodeling does not involve a reverse process because the myocardium undergoes largely irreversible histological changes. Although reverse remodeling may result in improvements in left ventricular (LV) function and cardiac chamber size, a significant amount of histologic damage remains present (13).

PHYSIOPATHOLOGY

In order to properly understand which are the current therapeutic targets that favorably impact in promoting reverse cardiac remodeling, it is necessary first to know the pathophysiological mechanisms underlying the process of pathological or adverse remodeling, which have been described more extensively in the post-myocardial infarction scenario (14).

ALTERATIONS IN THE MORPHOLOGY OF THE LEFT VENTRICLE

Geometric modifications are the main driver of LV remodeling and their progressive nature is explained by "Laplace's law". In other words, ventricular wall stress is inversely proportional to twice the LV wall thickness and is directly related to LV pressure and radius. Previously viable tissue is degraded in the early acute stages of myocardial infarction (MI), resulting in loss of contractile function and secondary increase in LV size, which increases oxygen consumption and wall stress. Cardiac workload increases weeks to months after MI as the heart strives to compensate for increased pre- and afterloads (15).

MYOCARDIAL HIPERTROPHY

Myocardial hypertrophy, a unique reaction to increased workload, generally refers to volume growth of cardiomyocytes that have reached the end of their differentiation. Pregnant individuals exhibit a natural transient mechanism that reduces wall stress and oxygen consumption to maintain cardiac output. Most importantly, this process does not cause any long-term damage; it can happen and then end. In contrast, overt heart failure is often caused by prohypertrophic molecular pathways that are chronically triggered by MI or pressure/volume overload. Physiological hypertrophy does not cause a particular pathogenic genetic pattern, as it involves sufficient vascularization, absence of fibrosis, and proportionally increases chamber size and wall thickness. (16)

On the other hand, pressure overload often results in heart failure related to both diastolic and systolic dysfunction, as well as marked fibrosis and disproportionately high increases in wall thickness relative to ventricular volumes, which activates closely related fetal genes (17).

MYOCARDIAL FIBROSIS

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MYOCARDIAL REGENERATION AND PROLIFERATION

Cardiomyocyte necrosis precedes the development of heart failure. Therefore, in the last two decades, attempts have been made to compensate for myocyte loss by enhancing regeneration of healthy myocardium. Zebrafish hearts and, shortly after birth, also mammalian hearts can fully regenerate after cardiac injury, an ability that, under certain circumstances, can be prolonged up to 4 weeks after birth. However, the pathophysiological principles underlying this complete regeneration are still not fully understood (20, 21).

INFLAMMATION

Accumulating evidence over time has confirmed that MI triggers an inflammatory response, which is primarily an orchestrated physiologic process (22). Necrosis and apoptosis are essential to this process and occur simultaneously, but result in significant changes. Apoptosis is a programmed cell death that does not involve the release of intracellular components and can occur intrinsically when a cell senses damage or extrinsically after inflammatory cells interact with so- called "death receptors". Necrosis is the main immediate phenotype of MI and is uncontrolled cell death accompanied by cell rupture. The released intracellular components activate the immune system through innate immune receptors. Inflammatory cells then invade and eliminate the necrotic cells, initiating a healing response and allowing appropriate scar tissue to form (23). Different types of inflammatory cells participate in this complex response at different times. Some cell subtypes promote inflammation, others mediate healing, and their differentiation and interactions are tightly regulated. Myocardial injury induces cardiac infiltration by neutrophils and macrophages, removes cellular debris, causes inflammation by production of proinflammatory cytokines, and attracts more proinflammatory cells. After a few days, neutrophils disappear and healing macrophages appear. T cells, on the other hand, control the activation of monocytes, which are essential for healing the heart. T-cell activation occurs in the lymph nodes draining the heart, for example through autoantigens released by necrotic myocytes 2. In the final "remodeling" phase, after solid scar tissue has formed, the non-infarcted myocardium gradually recruits inflammatory cells. Chronic activation of this cytokine and myocardial infiltration by inflammatory cells are also demonstrated in patients with heart failure. Experimental data on the pathological changes underlying this chronic phase and the clinical impact are very limited. However, the immune system may play a dual role. Thus, chronic proinflammatory conditions promote maladaptive remodeling, whereas proangiogenic factors may contribute to healing (18).

ISCHEMIA/REPERFUSION INJURY AND REACTIVE OXYGEN SPECIES

Coronary intervention in patients with ST-segment elevation myocardial infarction (STEMI) is very effective because it can restore the myocardium, reduce infarct size, and reduce the adverse effects of left ventricular remodeling. Complications that force reperfusion to restore myocardial blood flow may increase infarct size, referred to as reperfusion injury, depending on the duration of ischemia, pressure, and degree of residual blood flow (24). At the molecular level, succinate accumulated during ischemia is activated after reperfusion, a process that mediates the formation of reactive oxygen species (25). Prolonged production of oxygen radicals leads to the negative cycle of cardiac hypertrophy, cardiomyocyte death and remodeling through activation of matrix metalloproteinases (MMPs). These changes lead to chronic mitochondrial remodeling, decreased energy production, and ultimately pro-

mote the development of heart failure (26).

ENERGY METABOLISM AND MITOCHONDRIAL FUNCTION

Progressive metabolic remodeling is an important factor in the transition to heart failure after myocardial infarction (27). Although it remains to be determined whether adaptive (adverse) metabolic changes after myocardial infarction are a factor, it is clear that metabolic changes in left ventricular remodeling are more likely to develop and progress. During times of reduced oxygen supply (i.e., ischemia), the heart increases its glycogen stores and becomes more dependent on glycolysis to produce more energy from oxygen (14). The environment surrounding the muscle cells (e.g., stress, inflammation, hypoxia, etc.) and the availability of substrates regulate the above genes, leading to the need to convert carbohydrates to fatty acids and, at the same time, provide energy. A typical feature of prenatal hypoxic cardiac energy metabolism. Interestingly, deletion of certain genes can revert the mature heart to a disease state known as fetal genetic mode. Unfortunately, insulin resistance significantly reduces glucose utilization in cells, thereby activating mTOR and promoting the development of fibrosis and apoptosis. Increasing fat oxidation and reducing high glucose dependence prevents remodeling and improves myocardial efficiency, possibly restoring flexibility/homeostasis (35, 36). In addition to changes in substrate levels, elevated lactate accumulation leads to excess cytoplasmic calcium and, in turn, excess mitochondrial calcium, thus causing damage to the mitochondrial membrane, thus reducing energy production and pronecrotic and proinflammatory effects. . Molecules (28).

NEUROHUMORAL ACTIVATION

The sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS) evolved to maintain cardiovascular homeostasis. As angiotensin II continues to increase, the SNS and RAAS promote heart failure, vascular remodeling, and cell death in rat models. Furthermore, the level of SNS and RAAS activation in patients is associated with the development of heart failure and predicts the severity of the disease. The adverse effects of SNS and RAAS activation are the main focus of heart failure therapeutics (29, 30).

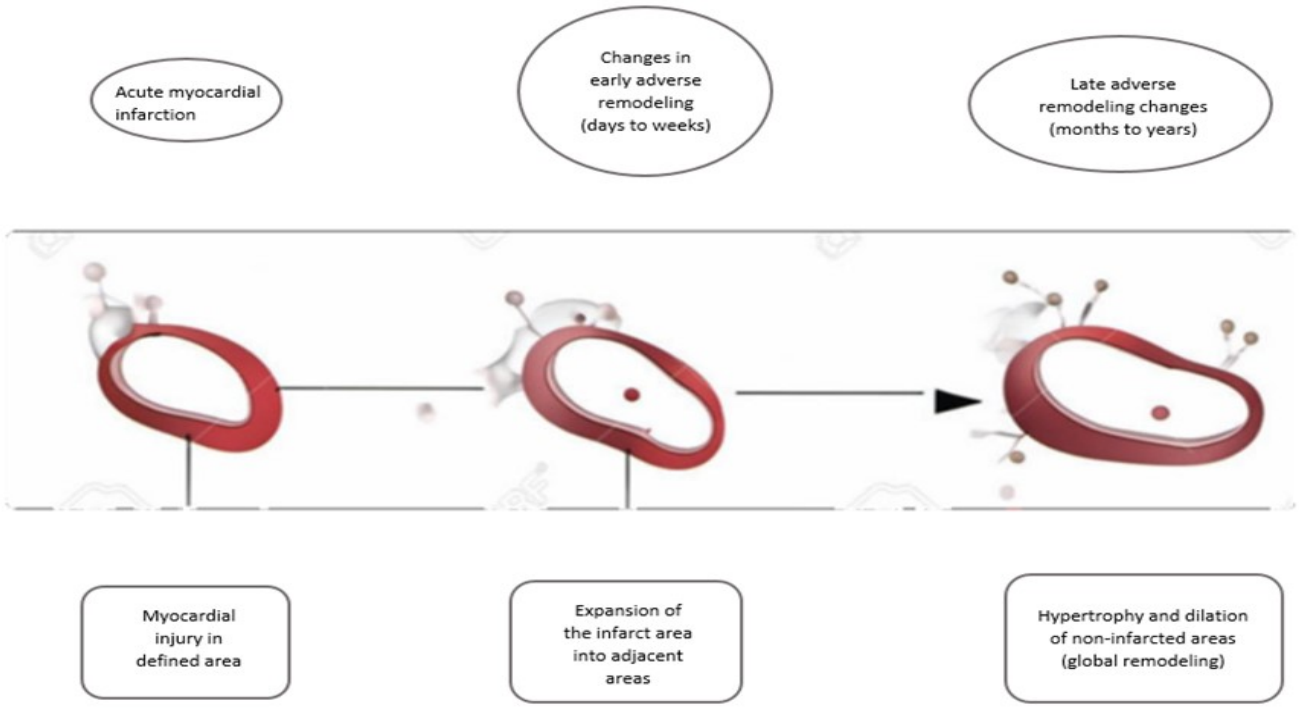
CARDIORENAL INTERFACE

The close connection between the heart and kidneys (called the cardio-renal axis) is key to the development and progression of heart failure. Several pathological processes, such as oxidative stress and inflammation are associated with chronic kidney disease (CKD) and heart failure, may also contribute to cardiorenal interactions; a growing number of experiments, including evidence using radiofrequency renal denervation (RDN), indicate a plausible cardiorenal interaction. (31,32)

NATRIURETIC PEPTIDES

Increased pressure and wall stiffness during myocardial infarction causes atrial and ventricular cardiomyocytes to produce natriuretic peptide (NP). Three isomers have been identified: A-type NP (ANP), B-type NP (BNP), and C-type NP (CNP). (33) Which act mainly as endocrine hormones, mediating diuresis, natriuresis, vasodilatation and inhibition of the SNS. and RAAS (34). In addition, some PNs, such as BNP and NT-proBNP, have good prognostic properties in post-myocardial infarction disease. Natriuretic peptide concentrations reflecting a profibrotic environment can be used to diagnose individuals at risk for remodeling, a group of patients who are currently not assessed by conventional imaging methods. In addition to endo-

crine effects, the nanoparticles counteracted the negative effects of prohypertrophic signals from angiotensin II and endothelin-1 and appeared to be an autocrine regulation of cardiomyocyte size (35). Type-A NPs inhibit collagen synthesis, a major cause of cardiac fibrosis. Interestingly, administration of fresh human BNP prior to coronary stent implantation appeared to protect against myocardial damage to some extent, demonstrating the therapeutic potential of NPs. (36)



Phases of post-infarction cardiac remodeling

CURRENT MANAGEMENT STRATEGIES MYOCARDIAL REVASCULARIZATION

The main objective of treatment of acute myocardial infarction is to restore myocardial perfusion and prevent necrosis by thrombolysis, percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG), thereby reducing the risk considerably. The benefit of cardiac remodeling by revascularization is to reduce infarct size and improve local and global function. Coronary revascularization with PCI is the standard treatment for patients presenting within 12 hours of symptom onset (37). In an observational study, Marek Grabka et al. Studies have shown that the likelihood of reverse cardiac remodeling is high in persons who have had a previous primary STEMI and are treated with primary PCI (38). In the absence of PCI, early thrombolysis should be considered, and several studies have shown that early thrombolysis can reduce the rate of ventricular wall stiffness. Current European and US guidelines recommend that all eligible STEMI patients begin fibrinolysis within 30 minutes of first medical presentation when PCI is not possible (39). Although the speed and success rate of myocardial revascularization with PCI is high, one-third of 1% of patients still die from fibrinolysis and develop heart failure and AMI. Up to one-third of patients will develop adverse cardiac remodeling despite the PCI approach (40).

EXERCISE-BASED CARDIAC REHABILITATION

After a heart attack, exercise-based cardiac rehabilitation is recommended in addition to medications to prevent the progression of cardiac remodeling.

The beneficial effects on the heart are due to the reduction of angiotensin II secretion, sympathetic activity and the distribution of catecholamine levels, in addition to improving the balance between MMP-1 and TIMP-1(41). This causes reverse remodeling, which reduces left ventricular diameter and increases left ventricular contractility. Furthermore, Zhang et al. showed that left ventricular changes are more likely to occur when an exercise program is initiated in the acute phase after a heart attack. Patients should receive an early physical training program for 8 to 12 weeks after a coronary artery syndrome (ACS) to reduce cardiovascular risk and readmission, according to the ESC 2020 Guidelines on cardiovascular exercise and exercise in patients with any evidence of heart disease.(42)

NEUROHUMORAL BLOCKADE: BLOCKADE OF THE SYMPATHETIC NERVOUS SYSTEM (SNS)

SNS inhibition plays an important role in therapeutic strategies following MI. US and European guidelines support the use of beta-blockers after MI as a class I indication. The long-term efficacy of carvedilol for morbidity and mortality has been demonstrated. In the CAPRICORN trial, carvedilol was compared with placebo in patients with LV EF ≤ 40% after myocardial infarction (43) . The effect of beta-blockers is to prevent the effects of catecholamine distribution, reducing heart rate and myocardial contractility, thereby reducing oxygen requirement. This prevents long-term interstitial fibrosis and significantly improves left ventricular remodeling (44). In the CAPRICORN Echo study, carvedilol was beneficial for ventricular remodeling: carvedilol-treated patients had a smaller increase in left ventricular end-systolic volume and a higher ejection fraction at 6 months after myocardial infarction compared with controls (45). In another study, Lee et al. compared the effects of propranolol and carvedilol on left ventricular volume and function in patients undergoing PCI after coronary artery disease. Similar changes in left ventricular end-diastolic volume were observed in both groups, suggesting that propranolol has the same effect as carvedilol. (46,47)

BLOCKADE OF THE RENIN ANGIOTENSIN ALDOSTERONE SYSTEM (RAAS)

In pivotal clinical trials, RAAS blockade has shown beneficial effects on mortality and cardiovascular events in patients with MI, especially in patients with low EF. Angiotensin-converting enzyme inhibitors (ACE inhibitors) block angiotensin II formation, thus preventing all its negative effects, improving left ventricular repair and improving heart failure progression. Current guidelines classify ACE inhibitor therapy as class I evidence based on several clinical trials demonstrating the benefit of ACE inhibitors on mortality and left ventricular systolic function in the case of myocardial infarction (48). Trials such as ISIS-4, GISSI-3, CCS-1, CONSENSUS-2, and SMILE focused on ACE inhibitor administration within the first 24 hours, but in recent trials (TRACE, AIRE) treatment was initiated within 48 hours after the acute event. Mortality after myocardial infarction was significantly reduced in all studies. A meta-analysis of all major studies supports the benefit of ACE inhibition in the early and late treatment of MI (49). Angiotensin II receptor antagonists (ARA II) are recommended as alternative therapy when patients do not tolerate or have contraindications to ACE inhibitors. By blocking AT1 receptors, ARA IIs can increase sodium and water retention, prevent cardiac hypertrophy and fibrosis, and improve post-infarction ventricular remodeling (50). Studies have shown that ARA IIs are as effective as ACE inhibitors after myocardial infarction. The OPTI-

MAAL clinical trial compared captopril and losartan, whereas the VALIANT study compared captopril and valsartan. Both ARA II have similar efficacy to captopril. Regarding ventricular remodeling, the VALIANT Echo substudy showed that treatment with captopril and valsartan produced similar changes in ventricular size and function after myocardial infarction (51). Compared with ACE inhibitors, ARA IIs have fewer side effects and are therefore better tolerated. In addition, this study shows that ARA IIs do not reduce the effects of bradykinin that seem to affect the cardiovascular system (52).

MINERALOCORTICOID RECEPTOR ANTAGONISTS (ARM)

It is currently recommended for the treatment of STEMI in ventricular systolic dysfunction with reduced LVEF (EF < 40%) and in patients with heart failure or diabetes treated with ACE inhibitors and beta-blockers. This ESC guideline recommendation is based on the results of the EPHESUS study that compared standard treatment with eplerenone administration in patients after myocardial infarction with left ventricular dysfunction, heart failure or diabetes. After an average follow-up of 16 months, reductions of 15%, 17%, and 21% were observed in all-cause mortality, cardiovascular disease, and sudden cardiac death each (53). The REMINDER study evaluated the outcome of initiating MRA within the first 24 hours in patients with STEMI without a history of heart failure. The primary endpoint was cardiovascular mortality, readmission or duration of first hospitalization due to heart failure, persistent ventricular failure, arrhythmia, and EF <40% or an increase in BNP/NT-proBNP 1 month or more after randomization. After more than 13 months of follow-up, the results showed that eplerenone was well tolerated and the primary endpoint decreased, as there was a significant reduction in natriuretic peptide levels. However, the ALBATROSS trial enrolled STEMI and non-STEMI patients and evaluated the benefit of early MRA in acute MI as adjunctive therapy (compared to standard care alone), even if it was heart failure or left ventricular failure. The primary outcome was death, recovered cardiac arrest, ventricular arrhythmia, implantable defibrillator indication, or new heart failure at 6-month follow-up. However, the ALBATROSS trial failed to demonstrate a benefit of early treatment with MRA compared with standard care in patients with MI. Experts believe that evidence alone is not sufficient to adequately assess the endpoints. The difference may be because the ALBATROSS trial included patients with STEMI and NSTEMI. In addition, analyses of the REMINDER cohort and the ALBATROSS STEMI subgroup showed a significant reduction in mortality in patients treated with MRA compared with patients treated with placebo (54).

ANGIOTENSIN RECEPTOR ANTAGONIST NEPRILYSIN INHIBITOR (ARNI)

ARNI (sacubitril/valsartan) is a new drug that simultaneously suppresses RAAS activity by blocking the AT1 receptor and suppresses bradykinin and natriuretic peptide depletion by suppressing neprilysin (55). This drug is currently considered one of the main treatments in the treatment of heart failure and reduction of EF because, as shown by the PARADIGM - HF trial, it significantly reduces disease and hospital mortality, the reduction was greater than with ACEI (56). The effects of NRAI in patients with acute MI were studied in the PARADISE-MI study, which compared sacubi-valsartan and ramipril in acute MI and left ventricular ejection fraction < 40% and/or signs of pulmonary edema. The results of this study showed that

sacubitril/valsartan did not reduce the risk of heart attack or first hospitalization for heart failure compared with ramipril, but had a significant effect on heart failure events (57). Furthermore, in a recent meta-analysis, Zhang et al. sacubitril/valsartan treatment after MI was shown to prevent ventricular remodeling, thereby improving cardiac function and reducing the incidence of adverse cardiac events (58)

INHIBITORS OF SODIUM-GLUCOSE CYTLE TRANSPORTER 2 (iSGLT2)

SGLT2 inhibitors, also called glyphozines, are among the novel therapies that are nowadays considered a cornerstone of management in heart failure. They have shown outstanding results at the cardiovascular level, first evidenced in the EMPA-REG, CANVAS, DECLARE-TIMI trials, in which iSGLT2 reduced mortality in a statistically significant way, all-cause mortality and hospitalization for heart failure (59-61). (59-61).

Empagliflozin and dapagliflozin reduced the incidence of recurrent infarction, which could be related to the ability to reduce ischemia reperfusion insult (62)

In MI, iSGLT2 exchanges the energy substrate from glucose to ketone bodies, free fatty acids and branched-chain amino acids, thus improving myocardial energy efficiency. Experimental evidence shows that iSGLT2 exerts cardioprotective effect in animal models in acute MI, improving cardiac function during ischemia, reducing infarct size, attenuating the development of heart failure. Early initiation and continuation of iSGLT2 after acute MI could favorably impact on the prevention of ventricular remodeling and progression to chronic heart failure. (63). Patients with acute MI have been relatively understudied in trials where the primary intervention has been iSGLT2. There are currently several ongoing trials including EMPACT-MI, EMMY and DAPA-MI that will evaluate the efficacy and safety of early initiation of iSGLT2 days after acute MI. (64)

STATINAS

Current international recommendations support the use of statins for secondary prevention of cardiovascular and cerebrovascular events. Recent research reveals that statins may help with cardiac remodeling by reducing cardiac fibroblast growth and extracellular matrix turnover. Experimental studies have shown that statins reduce LV dilatation after MI, thus minimizing cardiac remodeling. (65)

MODULATORS OF INFLAMMATION

Since inflammation is a prominent factor in ventricular remodeling following MI, several cytokines may be therapeutic targets in order to reduce myocardial inflammation. Amelioration of cardiac remodeling and the potential for development of heart failure could be achieved by blocking IL-1β signaling. The CANTOS trial evaluated canakinumab, a human monoclonal antibody that suppresses IL-1β. In people with prior MI who had elevated C-reactive protein (CRP), finding that it reduced circulating levels of CRP and decreased the risk of recurrent cardiovascular events compared with placebo (66). Several studies in mouse animal models have shown that after in vivo ischemia and nonischemic damage, cardiac systolic function is preserved by inhibition of NLR family pyrin domain 3 (NLPR3), the macromolecule that controls the activation of IL-1β and IL-18. Colchicine, a non-specific NLPR3 inhibitor, was administered and a significant decrease in infarct size was

observed.(67)

GENE THERAPY

A new treatment option that could have a major impact on adverse remodeling following MI is gene therapy. A novel peptide called angiotensin-(1-9) controls the RAAS. Gene therapy with angiotensin-(1-9) restored left ventricular systolic function after MI, restoring cardiac function, according to research by Fattah et al. using in vivo gene transfer in a mouse model of MI (68). Important regulators of unfavorable remodeling during myocardial infarction, in chronic heart failure, and when ventricular wall stress is increased are non-coding RNAs. The use of certain inhibitors to silence microRNAs in vivo arrests maladaptive remodeling and improves cardiac function (69). Extracellular plasma RNAs after myocardial infarction were linked to left ventricular remodeling characteristics in an investigation by Danielson et al. (70).

Different studies have shown that positive upregulation of miR-17 in diabetic mice improved left ventricular function and decreased infarct extension after acute myocardial infarction (71).

BONE MARROW CELL-DEPENDENT THERAPY

After MI, treatment with bone marrow-derived cells promotes transdifferentiation of progenitor cells into healthy cardiomyocytes, allowing repair of injured cardiac tissue. The REPAIR-AMI study evaluated the impact of intracoronary bone marrow-derived cell transplantation on post-MI remodeling and demonstrated a clear correlation between improved global LV function in patients undergoing acute MI and intracoronary infusion of bone marrow-derived cells. Transplanted patients showed a significantly lower incidence of mortality, reinfarction, and revascularization 12 months after receiving such transplantation (72). However, further studies are required as other studies revealed that treatment with bone marrow- derived cells had neutral results in patients with MI (73, 74).

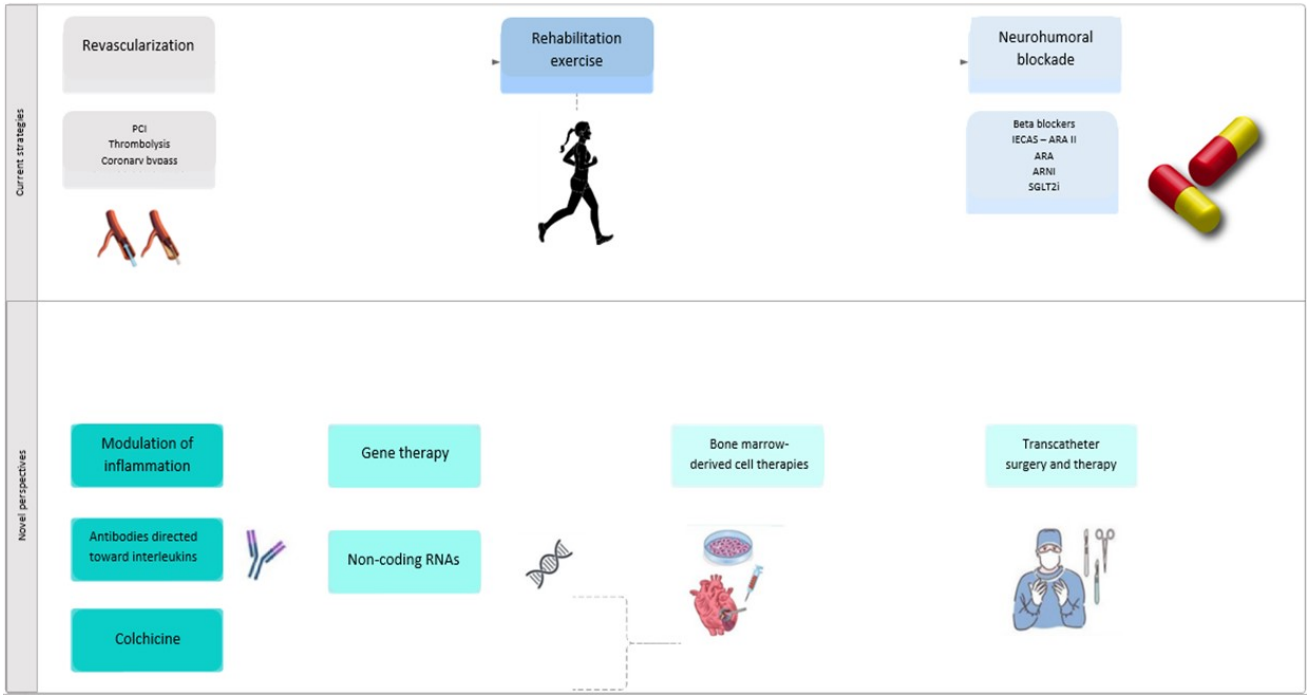
SURGICAL INTERVENTIONS OR VIA CATHETERS

Comparison of surgical techniques versus reperfusion therapy alone has shown no superiority in correcting deformed LV geometry with extensive regions of akinesia and aneurysms. In view of this, some heart failure patients with malignant ventricular arrhythmias or refractory symptoms may benefit from surgical techniques that reconstruct the ventricular shape. By plating the LV anterior and free wall scars against the right ventricular septal scar, patients with chronic anteroseptal infarction can undergo minimally invasive transcatheter operations that exclude the anteriorly scarred myocardium from viable tissue (14). By reducing LV volume and restoring LV conical shape, this approach could improve LV systolic function.(75)

CONCLUSIONS

Adverse remodeling is a cause of cardiac failure and increases patient mortality, also influencing operating costs in health systems. Impacting the underlying pathophysiological mechanisms has been shown to promote reverse remodeling, which is nothing more than attempting to recover previous cardiac functionality with different therapies that have been shown to have a positive impact, such as SGLTi2, ARNI, ARM, and beta-blockers. Different strategies focused on MicroRNAs, molecules that act at the level of inflammatory mechanisms and tissue replacement with bone marrow cells are under development, with promising re-

sults, as we better understand the mechanisms of myocardial remodeling, better management strategies will emerge.



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