

Ventricular Remodeling after Myocardial Infarction: Concepts and Clinical Implications

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Remodeling process after acute myocardial infarction (AMI) is clinically characterized by ventricular cavity increase. In the acute phase, ventricular dilation is a result of infarction expansion process, whereas late cavity dilation is the result of the eccentric hypertrophy process.

Ventricular remodeling plays a key role in the pathology of post-infarction ventricular dysfunction. When reacting to aggression, the genetic, structural, and biochemical changes arising from that process will result in the deterioration of the functional ability of the heart in the long run. Signs and symptoms of the onset of heart failure and/or sudden death will result. The mechanisms that have been proposed for the onset of ventricular dysfunction are complex, but the ones to be pointed out are changes in: calcium transit; beta-adrenergic pathway; contractile proteins; increased cell death; collagen accumulation; methaloproteases; higher oxidative stress; energy deficit; cytoskeletal, membrane and matrix proteins; and ventricular geometry. Additionally, remodeling is associated to higher prevalence of cardiac rupture, arrhythmia, and aneurysm formation after infarction.

Remodeling is therefore associated to impaired post-infarction prognosis. As a result, a better understanding of such process is critical since remodeling course can be modified through a number of therapeutic interventions.

Background

The word 'remodeling' was used for the first time in association with myocardial ischemia in 1982 by Hockman and Buckey while addressing the replacement of necrotic tissue infarcted with healing tissue¹. In 1985, Janice Pfeffer was the first researcher to use the word 'remodeling' in its current meaning. Remodeling was used to characterize the increase of left ventricular cavity in an experimental model in rats². In the following years, the word was occasionally used in articles on morphological changes following acute myocardial infarction (AMI). In 1990, Pfeffer and Braunwald³ published a review on post-AMI remodeling. The expression was created to characterize the post-infarction morphological

Key words

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changes, specifically ventricular cavity increase. In that article the authors emphasized that the remodeling process resulted in ventricular dysfunction³. In the years that followed, the word 'remodeling' was widely used to encompass a large variety of clinical scenarios. In the year 2000 an international forum defined remodeling as molecular, cellular, and interstitial cardiac variations that have clinical manifestations through changes in heart size, mass, geometry and function as a response to a given aggression. (Figure 1)^{4,5}.

Remodeling characterization after AMI

Interfibrillar collagen disintegrates concurrently to myofibrils necrosis. The region is more bound to distension due to the loss of that support tissue; and consequently, more susceptible to deformations. Therefore, necrotic areas may slide and realign myocites on the infarcted wall. As a result, affected area thinning and cavity dilation are observed. That acute ventricular dilation – characterized by infarcted wall thinning an distension – is defined as infarction expansion^{1,6}.

Chronically, it must be taken into account that in normal hearts both systolic and diastolic tension are at maximal value at midventricle, intermediate level at the base, and lowest level at the apex. As a result of post-infarction expansion, the ventricle loses its elliptical form and takes up spherical configuration. Under this new format, apical parietal tension is significantly increased to reach midventricle level, with midventricle

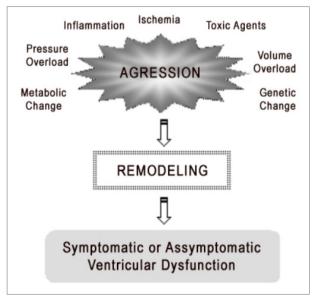


Figure 1 - Natural history of ventricular remodeling.

level also being increased. In addition to that redistribution, diastolic parietal tension is shown to be significantly higher than systolic tension. Stress increase is believed to stimulate sarcomeres replication, preferably in a serial fashion. As a result of the interaction of those factors, the ratio cavity radium/wall thickness is typically increased, thus characterizing the eccentric ventricular hypertrophy^{3,4,7}. Therefore, chronic ventricular dilation secondary to eccentric hypertrophy is the adaptation to allow for ventricular function maintenance, opposedly to parietal stress increase (Figure 2).

Therefore, following acute myocardial infarction the remodeling process is clinically characterized by ventricular cavity increase. In the acute phase, ventricular dilation is the result of the infarction expansion process, whereas late cavity dilation is the result of the eccentric hypertrophy process.

Consequences from remodeling

As a result of infarcted wall thinning and growth in AMI acute phase, the concept that prevails is that expansion predisposes the onset of ventricular rupture, also contributing with the anatomic substratum for future aneurysm formation³.

In regard to the functional aspects, we should consider that ejection volume reduction is expected as a result of post-AMI muscular tissue loss, with LV final systolic and diastolic volume increased. The process results in diastolic pressure (pre-load) increase and ventricular dilation. Contractility tends to be restored through Frank-Starling mechanism action, thus restoring, at an early stage, ventricular filling pressures.

Chronically, however, ventricular remodeling plays a key role in the pathophysiology of ventricular dysfunction. When reacting to injury, the genetic, structural, and biochemical

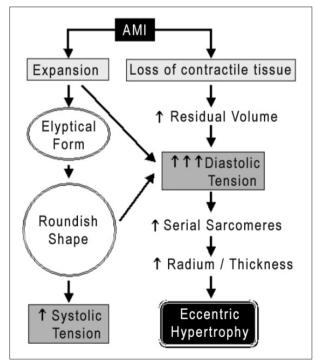


Figure 2 - Chronic phase of left ventricle remodeling.

changes arising from that process will result in the deterioration of the functional ability of the heart in the long run. Signs and symptoms of the onset of heart failure and/or sudden death will result^{3-5,7}.

Although the concept that ventricular remodeling results in ventricular function progressive deterioration still prevails, the mechanisms that trigger such phenomenon have not been fully understood to this point in time. Irrespective of any stimulus, one of the most outstanding characteristics in remodeling is the change in the expression pattern of a number of proteins, with an increase or the re-expression of fetal period genes. The causes and possible benefits or drawbacks for such behavior have not been fully understood. It is well accepted, however, that fetal genetic expression is both a marker and can also be related to the very mechanisms involved in remodeling process progress, up to the onset of ventricular dysfunction^{5,8}.

Some of the potential factors involved in the progressive deterioration of ventricular function in the remodeled heart will be discussed further on.

Calcium transit

Calcium transit through the sarcoplasmatic reticle is an active, complex process that involves a number of components. Calcium membrane systems as well as calcium intracellular systems (L-type channels, rianodin, calsequestrin) regulate the amount of calcium offer to contractile proteins in the contraction process. Likewise, calmodulin kinase activation and phospholambam phosphorilase stimulate the enzymes (SR-Ca⁺⁺-ATPase or SERCA-2) that are responsible for the highest calcium uptake through the sarcoplasmatic reticle, thus promoting improved relaxation⁹.

Evidence is available on a number of changes in calcium transit under ventricular remodeling and dysfunction, as for instance changes in the L-channels, rianodin receptors, reduced calsequestrin and calmodulin kinase activity, phospholambam phosphorilase reduction and SERCA-2 activity reduction⁹.

Changes in the beta-adrenergic pathway

The interaction of catecholamines and their receptor, followed by the conversion of extracellular stimulus into intracellular response, is defined as the beta-adrenergic pathway¹⁰. Mediated by regulating protein (protein G), the extracellular stimulus acts on $\beta1$ and $\beta2$ receptors which, in their turn, interact with the effector by activating or inhibiting the production of 3′5′cyclic adenosine monophosphate (cAMP) and kinases. Adenyl cyclase activity is modulated by two G proteins: the Gs, with the ability to stimulate adenyl cyclase activation and Gi, that can inhibit such activation. The activation of G proteins and cAMP/kinase complex promotes cytosolic calcium increase, thus resulting in a positive inotropic effect.

A number of changes have been identified in the beta-adrenergic pathway under the pathologic conditions remodeling occurs: β1 receptors concentration reduction, β2 receptors concentration increase, lower levels of Gs protein, higher levels of Gi protein, and adenyl cyclase activity reduction. Therefore, as it occurs with calcium transit, beta-

adrenergic pathway will most likely play a key role in cardiac function deterioration in the remodeled heart¹⁰.

Changes in contractile proteins

Ventricular remodeling is characterized by changes in the most important contractile protein – myosin. Myosin contains one pair of heavy chains (α and β) and two pairs of light chains. Depending on chain composition, three isoenzymes may be identified (V1, V2 and V3) in the myocardium of different species. Those isoenzymes contain the same pairs of light chains, the only difference being in regard to heavy chains composition ($\alpha\alpha$ in V1, $\alpha\beta$ in V2 and $\beta\beta$ in V3). Myosin ATPase capacity depends on native sites in the heavy chains, with α fraction showing the highest ATPse capacity. Therefore, isoenzyme composition determines myocyte contractile capacity. In addition to the predominance of myosin light chains fetal form during remodeling, V3 isoform is typically increased, associated to V1 isoform reduction8.

Cell death

Three myocyte death mechanisms may be identified: apoptosis, or programmed cell death; autophagic; and necrosis. The role played by those three cell death mechanisms in cardiac function deterioration has been studied in a number of models¹¹. However, their contribution for or involvement in ventricular dysfunction and remodeling is still controversial. In spite of that, myocyte progressive loss is accepted as present in the different ventricular remodeling models and may play a role in function deterioration following AMI¹².

Fibrosis

Myocytes make up only 30% of the total number of myocardial cells. Complex, organized collagen connections surround and interconnect all those structures. Interstitial collagen fibers are predominantly of types I and III (95% of total collagen). Interconnections major functions are: apoptosis regulation; pathologic deformation resistance; structural alignment maintenance; cardiac distension regulation; and force transmission during cardiac fiber shortening. Collagen tissue is, therefore, a key modulator both for diastolic and systolic cardiac function¹³.

A solid body of evidence is available to show post-AMI collagen accumulation (fibrosis) in infarction remote areas. Under such condition, fibrosis is associated to ventricular function deterioration¹³.

Changes in metalloproteinases

Collagen fibers are typically firmly juxtaposed, with strong chemical binding. They are resistant to the degradation caused by most proteinases. Some enzymes, however, have collagenolytic activity. Among those, the metalloproteinases stand out. Those enzymes are in their inactive form (latent proenzyme), and may be activated by a number of stimuli: mechanic; ischemic; angiotensin II; endothelin 1; catecholamine; tumoral necrosis factor; and interleukin 1 among others¹⁴.

Interfibrillar collagen connections breakdown may have quite a number of consequences both in ventricular architecture

and function. Increased metalloproteinases activity in rats with acute myocardial infarction, for instance, was associated to progressive ventricular dilation. Likewise, pharmacological inhibition of metalloproteinases in AMI animals attenuated remodeling process, with resulting functional preservation^{15,16}. Data available do suggest, therefore, that metalloproteinases play a key role in ventricular remodeling and dysfunction secondary to AMI.

Increased oxidative stress

Enough evidence is available to show that AMI results in increased oxidative stress. Reactive Oxygen Species (ROS) come from different sources. Among them, the following stand out: mitochondrial electron transporters; NADPH oxidase system; cyclooxigenase acticity; cytochrome P450; glucose oxidase; xanthine oxidase; lipooxigenase; and catecholamine degradation¹⁷. Reactive species activate a number of cell signalers which, in the acute phase, contribute for inflammatory process and healing of infarcted region. Chronically, however, oxidative stress would induce remodeling since it results in mitochondrial dysfunction, metalloproteinases activation, fibrosis, hypertrophy and cell death¹⁸⁻²⁰.

Energy deficit

Another potential factor in cardiac function changes in the remodeled heart is energy deficit. It results from the unbalance between oxygen offer and consumption. Under normal conditions, free fatty acids (FFA) are a major energy substratum for the heart, with a 60% to 90% contribution. FFA metabolites are involved in ATP production in mitochondrial electron transporters through β-oxidation. Energy produced is stored and transported in the form of phosphocreatine. A number of energy metabolism changes have been identified in remodeling. They are expressed through energy production reduction: reduced use of FFA and increased use of glucose as energy substratum, β-oxidation reduction, and mitochondrial functional changes. Those changes are associated to lower levels of phosphocreatine. As mentioned earlier, that is how ATP is stored^{21,22}. As a result, all myocardial proteins with ATPase capacity - as those in myosin heavy chain and those responsible for calcium uptake through the sarcoplasmatic reticle - may present functional deficit and deterioration both in systolic and diastolic function⁵.

Renin-angiotensin-aldosterone system (RAAS)

Renin-angiotensin system^{4,5,23,24} deserves to be pointed out in the pathophysiology of post-AMI remodeling process. The activation of that system stimulates the intracellular signaling pathway with resulting myocyte increase and fibroblast protein synthesis, leading to cell hypertrophy and fibrosis. Other effects would be increased vessel permeability; growth factor activation; metalloproteinases activation; hemodynamic overload through vasoconstriction and water retention; increased oxidative stress; and direct cytotoxic effect leading to cell death through necrosis or apoptosis. Therefore, the renin-angiotensin system blocking acts as an attractive strategy for the treatment of post-infarction remodeling as discussed further on.

Other changes

Membrane, matrix, and cytoskeletal changes may also be associated to the remodeling process. Remodeled hearts have been reported to show changes in tubulin, desmin, titin, integrins, ADAM (A Desintegrin And Metalloproteinase), membrane metalloproteinases, are associated to ventricular dysfunction²⁵⁻²⁷. Therefore, changes in cytoskeletal, membrane and cell matrix proteins may be involved in the pathophysiology of ventricular dysfunction associated to post-AMI remodeling.

Additionally, hypertrophy is a major mechanism through which myocytes adapt to a given stimulus. In recent years, post-infarction experimental studies have identified that myocardial contractility remained unchanged in infarcted animals. The phenomenon occurred in spite of left ventricular dilation, which was associated to dysfunction signals and heart failure, as pulmonary congestion. The authors concluded that although infarcted and non-infarcted animals' muscle have the same intrinsic capacity to generate force, infarcted rats presented depressed ventricular function. Therefore, based on the geometric changes that took place, remodeling itself could compromise cardiac global function^{28,29}.

Ventricular remodeling has, then, shown to involve a number of morphological changes in response to a given stimulus or injury. At a first moment, the process may be adaptive, but in the long run, one of the consequences of remodeling would be the onset of progressive ventricular dysfunction. The mechanisms responsible for functional deterioration are not yet fully understood, but they may include genetic, structural, biochemical, and energy changes.

Ventricular Remodeling Determining Factors

Post-AMI ventricular remodeling process is not homogeneous. Four factors interfere in the prevalence and intensity of that process:

1) Infarction morphologic characteristics.

Although remodeling may be present at ischemic injuries of different sizes, its predominance has been observed in large size infarctions. Likewise, it seems a minimum injury size (16-20%) is a pre-requisite for remodeling to occur. Another factor is relative to the fact that due to large ventricular curvature and to anteroapical thinning, remodeling frequency occurs in that area, typically in transmural infarctions^{3,30,31}.

2) Healing Characteristics.

In the early post-AMI period significant collagen volume increase is observed in the infarcted area. At a first moment, Type III collagen is increased. Type III is known to have lower resistance to deformation of Type I collagen – harder, and predominant in normal hearts. With time, Type III collagen is reduced, and Type I grows higher. Newly formed collagen is admittedly less hard than mature collagen. Associated to the predominance of Type III collagen, that will determine the potential vulnerability of healed area to possible deforming forces. Therefore, AMI cicatrization is an intervention-sensitive dynamic process³². For illustration purposes: the administration of NSAIDS or corticosteroid resulted in

slower healing, which turned the area more susceptible to deformations after marked ventricular expansion3.

3) Hemodynamic Stress.

Load condition fluctuations of the working heart are known to occur relative to hemodynamic stress during infarction. It has been well documented in the literature that cardiac overload interferes in the remodeling process³⁻⁵. Experimental studies have shown, for instance, that maneuvers such as aortic constriction, metoxamin infusion and early physical exercise have resulted in larger ventricular dilation when control animals are compared to. Likewise, hypertensive humans have presented a more intense remodeling process³.

4) Modulators.

Infarction is most typically characterized by increased levels of a number of modulators, such as: angiotensin II; endothelin 1; catecholamine; tumoral necrosis factor; interleukin 1 and 6; transforming growth factor beta-1; and insulin-like growth factor 1 (IGF-1). It has been admitted that those increased levels play a pathophysiological role, since the different modulators regulate initial infarction events such as inflammatory reaction and healing. In addition, they result in hemodynamic and inotropic effects that act as counterparts to the loss of contractile tissue for the hemodynamic stabilization of patients. Under physiologic situations, the levels of modulators go back to normal within a week's time. In some cases, however, those levels may be kept high. Experimental models have shown that modulators increased levels may both trigger and regulate cardiac remodeling^{33,34}.

Ventricular remodeling natural history

After infarction, approximately 50% of patients develop some degree of left ventricular dilation. From those, 50% of patients develop progressive ventricular chamber increase, while 50% are kept stable. From those without dilation in the acute phase, a non-defined number will present remodeling after some weeks, months, or years after the ischemic insult³⁵.

Diagnosis

Post-infarction remodeling clinical diagnosis is based on the identification of left ventricle cavity enlargement. In order to reach diagnosis, the most commonly used methods are echocardiogram, ventriculography, and MRI. It has been admitted that MRI provides better sensitivity for the detection of changes that occurred in left ventricular cavity. However, due to costs and technical requirements, its clinical application is still limited. As a result, in clinical practice and in major clinical trials, the most commonly used method for remodeling diagnosis is echocardiogram³⁶.

Another possibility for diagnosis - for the time being used only in experimental models and isolated clinical reports - is based on the detection of cell markers that characterize fetal genotype. Among those, the following are to be mentioned: changes in myosin heavy chain, with $\alpha\text{-myosin}$ reduction and $\beta\text{-myosin}$ increase, $\alpha\text{-actin}$ increase; natriuretic peptide increase; GLUT4 reduction and GLUT1 increase; SERCA-2a reduction and angiotensin converting enzyme increase³-5.8,37.

Differential diagnosis

Muscle bundle sliding – typical in abrupt, intense infarction – may result in precordial pain of variable magnitude. Another aspect to be considered is that although the expansion does not change necrotic tissue volume, fiber sliding increases infarcted myocardial surface. Therefore, ST segment elevation may be intensified in already compromised leads, or else, changes may occur in ST segment leads that were not compromised at a first moment. Additionally, in extreme cases, some blood may be retained in the expanded region during systole, thus resulting in systolic volume reduction and hemodynamic compromising³⁸.

As a result, major differential diagnosis for infarction expansion is infarction extension. (Table 1). While expansion is a frequent event (50%), extension occurs in less than 20% of AMI cases. Expansion is more frequently observed on the first days after infarction in anterior wall transmural large size infarctions. Extension may occur any time. However, a major distinction between the two complications is that extension is associated to new enzyme increase, since it implies new necrotic foci³⁸.

Remodeling prediction factors

As mentioned earlier, a number of factors favor the onset of remodeling, the major ones being: large, transmural, anterior infarctions; ejection fraction decrease; absence of or inefficacy of reperfusion; no-reflow phenomenon; early coronary reocclusion; high blood pressure; and the use of NSAIDS and corticosteroid in AMI acute phase (Table 2)^{3,4,35}. More recently, experimental data have suggested that smoking may intensify post-AMI remodeling³⁹. Likewise, a recent clinical trial has suggested that high baseline glycemia may also predict remodeling⁴⁰. On the other hand, small size, subendocardial infarctions, inferior infarctions, presence of maintained reperfusion evaluated by ST segment resolution, permeable microcirculation, previous angina, lack of comorbidities and certain drugs prevent the onset of remodeling^{3,4,35,41-43}.

Table 1 - Differential Diagnosis: AMI Expansion and Extension

Variables	Expansion	Extension
Precordial pain is present	Presentation possible	Presentation possible
Changes in ECG	Presentation possible	Presentation possible
Hemodynamic Instability	Presentation possible	Presentation possible
Prevalence	50-70%	20%
AMI Type	Transmural	Irrespective of type
Preferred site	Anterior wall	Irrespective of wall
Infarction size	Large	Irrespective of size
Point in time	First days	Irrespective ofo period
Enzyme increase	No	Yes

ECG: electrocardiogram; AMI:Acute Myocardial Infarction. Adapted from Hutchins³⁸

Table 2 - Post-AMI remodeling predictors

Favor remodeling	Attenuate remodeling	
Large Size Infarctions	Small Size Infarctions	
TransmuralInfarctions	SubendocardialInfarctions	
Previous Infarctions	Lower/Lateral Infarctions	
↓ Ejection Fraction	Fração de ejeção preservada	
No reperfusion	Efficacious reperfusion	
Early reocclusion	Coronary permeability kept	
Microcirculation compromised	Microcirculation untouched	
No collaterals	Functioning Collateral Circulation	
SAH, DM, Smoking	Previous Angina	
Medications(NSAIDs, corticosteroids)	Medications (ACEI)	

SAH - Systemic Arterial Hypertension; DM - Diabetes Mellitus; NSAIDS - Non-Steroidal Anti-Inflammatory Drugs; ACEI - Angiotensin Converting Enzyme Inhibitors

Controversies about post-AMI remodeling

Although remodeling is one of the most comprehensively studied topics in recent years, a number of issues are still controversial.

Firstly, infarction is characterized by cardiac tissue death, which is replaced by healing tissue. Therefore, conceptually, every infarcted heart changes its composition, which means to say, suffers remodeling. Clinically, however, as already discussed, the word 'remodeling' is commonly used after infarction to mean ventricular cavity pathologic enlargement.

Another aspect to be considered is that the word 'remodeling' is commonly used to characterize pathologic adaptations. But such concept not always applies. As discussed earlier, 50% of patients develop ventricular cavity enlargement in the post-infarction acute phase. Only 50% of those patients, however, presents progressive cavity enlargement and impaired ventricular function. The other patients are kept stable, both morphologically and functionally, which suggests that in those patients cavity enlargement may be adaptive, with no deleterious consequences. Additionally, a number of transgenic animal models present ventricular dilation and hypertrophy in response to different overloads, but no signs of ventricular dysfunction or survival compromising⁴⁴. Evidence accumulated to this point in time, therefore, suggest that under certain situations remodeling may be adaptive and contribute for ventricular function maintenance in response to certain stimuli (adaptive or physiologic remodeling). În addition, it has been admitted that this adaptive process would be modulated by different cell signaling pathways (phosphatidylinositol-3 kinase) of the pathways involved in pathologic remodeling (phospholipase C, protein kinase C and calcineurin)⁴⁵⁻⁴⁷.

Finally, it is important to point out that remodeling is a very complex process, and implies genetic, cellular and molecular changes. Morphological changes as post-infarction cavity enlargement, for instance, are only one way clinicians

use to reach diagnosis and stratify the phenomenon. Until recently, strategies aiming at remodeling reversion focused morphological changes regression exclusively. As a result, up to this point in time doubts are still pending whether the regression of morphological changes is associated to the reversion of genetic, biochemimal, and cellular reversion. However, more recent data have suggested that heart failure patients submitted to a few intervention procedures showed that wall thickness and left ventricle cavity volume reduction were associated to: myocite size reduction; calcium transit restorarion; cytoeskeletal and beta-adrenergic pathway improvement; collagen volume reduction; and possible changes in the intracellular pathways that are responsible for remodeling⁴⁸. Remodeling clinical reversion, therefore, seems to be a real event, and is associated to the reversal of processmodulating pathophysiologic changes.

Remodeling prevention - attenuation - reversion

Due to its ability to highly reduce infarction size in regard to transmurality, myocardial reperfusion is the best prevention action against remodeling. ASA is the best choice anti-inflammatory in AMI acute phase since it does not interfere in healing characteristics. Another measure is left ventricle parietal stress; therefore, blood pressure increase should be avoided in AMI acute phase.

As for specific medications, experimental studies have shown that early use of angiotensin converting enzyme (ACEI) inhibitors attenuated remodeling. (2,49) That was confirmed through clinical trials. (50,51) Likewise, the early administration of angiotensin II AT1 receptor antagonists in rats atennuated remodeling and reduced post-AMI mortality rate. (52) Later, clinical trials did not find any difference in ARAII action as compared to ACEI after infarction. (53) Although the use of beta-blockers and aldosterone antagonists by ventricular dysfunction patients with < 40%

ejection fraction is also associated to better prognosis, ^(54,55) the effect of those drugs on patients with no ventricular dysfunction after infarction is not yet known. Finally, it should be considered that revascularization in patients with a hibernating myocardium may be associated to lower remodeling. ^(56,57) Other preventive therapeutic approaches for remodeling prevention, attenuation or reversion after infarction – such as cell regeneration; vasopressin antagonists; natriuretic peptides; ventricular synchronization; mechanic devices; nitrates and statins – still need confirmation through clinical trials.

Conclusion

Ventricular remodeling is a relatively common post-AMI event. The relevance of remodeling is associated to the fact that in addition to resulting in higher cardiac rupture prevalence, arrhythmia and aneurysm formation, the process may modulate the onset and the progression of ventricular dysfunction, heart failure and the outcome of death following infarction. Also to be considered is the fact that this process is not homogenous in AMI patients. Therefore, patients with diagnosed remodeling or under high risk of developing remodeling must be treated in an aggressive fashion in order to prevent, attenuate, or even revert the process.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any graduation program.

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