International Journal of Chemical and Biochemical Sciences
(ISSN 2226-9614)

Journal Home page: www.iscientific.org/Journal.html

An Overview on Left Ventricular Remodeling after Myocardial Infarction

*Ahmed Shafeea Ammar, Mohammed Mostafa Al-Daydamony, Mahmoud Ali Ahmed Elabyad *, Mohammed Salah Ghareeb*

Cardiology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt

Abstract

Myocardial infarction has traditionally been divided into ST elevation or non-ST elevation myocardial infarction; however, therapies are similar between the two, and the overall management of acute myocardial infarction can be reviewed for simplicity. Acute myocardial infarction remains a leading cause of morbidity and mortality worldwide, despite substantial improvements in prognosis over the past decade. Progress is a result of several major trends, including improvements in risk stratification, more widespread use of an invasive strategy, implementation of care delivery systems prioritising immediate revascularisation through percutaneous coronary intervention (or fibrinolysis), advances in antiplatelet agents and anticoagulants, and greater use of secondary prevention strategies such as statins. Heart failure secondary to myocardial infarction (MI) remains a major source of morbidity and mortality. Long-term outcome after MI can largely be defined in terms of its impact on the size and shape of the left ventricle (i.e. LV remodeling). Three major mechanisms contribute to LV remodeling: (1) early infarct expansion, (2) subsequent infarct extension into adjacent non infarcted myocardium and (3) late hypertrophy in the remote LV. Future developments in preventing post-MI heart failure will depend not only on identifying drugs targeting each of these individual mechanisms, but also on diagnostic techniques capable of assessing efficacy against each mechanism.

Keywords: Left Ventricular Remodeling, MI, CAD.

Full length article **Corresponding Author*, e-mail: *Drelabyad91@yahoo.com*

1. Introduction

Pfeffer et al. firstly described term 'LV remodeling 'in the 1980's to describe progressive LV dilation and impairment of cardiac function following chronic coronary artery occlusion [1]. The term has since been applied to all LV morphological change in both health and disease [2]. Remodeling results from chronic alterations in hemodynamic loading conditions and is characterized by geometric and structural changes. This results in altered myocardial architecture and LV chamber configuration with a subsequent impact upon function [3]. It is now clear that overarching pathological or physiological environment determines nature in which LV remodels and there is general acceptance for a system of classification. With very few exceptions, development of concentric geometry/hypertrophy can be attributed to increased cardiomyocyte thickness in response to systolic pressure overload, whereas eccentric geometry/hypertrophy is caused by myocyte lengthening as an adaptation to volume overload [4] Classification of LV remodeling is dependent on the measurement of a number of parameters, namely LV mass, LV volume and relative wall of LV wall thickness to chamber radius. The development of LV hypertrophy (i.e. increased LV mass) has important implications in evolution of pathological LV remodeling [3].

2. Left ventricular remodeling following acute myocardial infarction

2.1. Phases of Post-infarction Remodeling

Post-infarction remodeling has been arbitrarily divided into an early phase (within 72 hours) and a late phase (beyond 72 hours). The early phase involves expansion of the infarct zone, which may result in early ventricular rupture or aneurysm formation. Late remodeling involves the LV globally and is associated with time-dependent dilatation, mural hypertrophy, and distortion of ventricular shape [5].

I. Infarct zone expansion

This process is defined as "acute dilatation and thinning of the area of infarction not explained by additional myocardial necrosis" [6].This thinning is a consequence of lateral side to side slipping of myocytes past one another in the transverse plane (due to dissolution of the collagen struts) resulting in reduction in the number of myocytes across the infracted region [7]. Infarct extension, by contrast, is defined

as an increase in the size of the noncontractile region in the sitting of a continuing ischemic insult [8]. Thus, the clinical diagnosis of infarct expansion is made with echocardiographic determination of infarct lengthening without enzyme evidence of further myocardial necrosis [9]. Expansion of the endocardial segment occurs as early as 10 minutes after coronary occlusion and progress within the next 1 to 2 weeks [10]. Excessive infarct expansion can lead to HF, LV aneurysm formation or early cardiac rupture [8]. Early rupture is caused by extremeinfarct expansion in which the expanded region is so thin that it is not capable of maintaining the integrity of the ventricular wall before complet scar formation [11]. Development of an aneurysm early in the course of anterior MI offers a much higher mortality rate [12].

II. Left ventricular dilatation

It is well recognized that survivors of MI can demonstrate pronounced cavity enlargement [13].The development of LV dilatation (that is not explained by an elevated filling pressure or reinfarction) is the main finding of LV remodeling and is one of its major determinants of a bad outcome [13]. Jermey et al. [14] found a 42% increase in LVEDV over 6 months in patients with their first anterior MI [14]. After coronary artery ligation in the rat, there is early thinning and distension of both the infracted (infarct expansion) and the non-infarcted myocardium (passive distension) [15]. However, dilatation of the non-infarcted region continues for a more protracted period and is more likely to be the major contributor to late phase of ventricular enlargement [16]. The increase of LV volume early after MI is attributed mainly to elongated LV circumference and to a lesser extent to increase in the LV sphericity. Late, increase in LV volume is only result of further distortion of shape of the LV to a more spheric configuration [16]. Mitchell et al. showed that of the 88 ml early (2 weeks) post infarction increase of the LVEDV, 66 ml was attributed to an elongated

LV diastolic circumference and 22 ml to increase sphericity. The increase of the LV diastolic circumference was due to elongation of non-contractile segment (infarct expansion) and contractile segment (passive distension). In same study , most of late (1 year) post infarction increase of the LVEDV was due to increase of the LV sphericity; total LV circumference did not change significantly because increase in length of contractile segment was offset by decrease in length of non-contractile segment. Of note, patients with significant late LV enlargement (LVEDV increase > 20 ml) had significant increase of both sphericity and in diastolic LV circumference secondary to elongation of the contractile segment [17]. In A, there is increased volume as a result of increased circumference of infracted, non-contractile segment. In B, marked increase in volume results from increased circumference and spherecity. The late increase in circumference is due to lengthening of contractile tissue; note that increase in spherecity results from a rounding out of sharp abnormalities in contour at margins of infarct. Stippled lines= endsystole, solid lines: end diastole [17].

III. Mural hypertrophy

After AMI, there is compensatory eccentric LV hypertrophy of no infarcted area. Eccentric hypertrophy involves serial deposition of new sarcomeres which results in elongation of cells without an increase in cell thickness. This process tends to return wall stress induced by LV dilatation toward normal. [18]. However, increase in cell length without a corresponding increase in myocyte diameter would lead to a further increase in diastolic wall stress [19]. Cardiac hypertrophy is stimulated by a variety of neurohormonal (e.g., catecholamines, RAS, aldosterone, endothelins,..), local growth promoting peptides (FGF, IGF-I,..) and mechanical stretch induced by elevated wall stresses transduced through a common mechanism involving activation of protein kinase cascades [20]. After coronary ligation in rats, hypertrophy of surviving myocytes occurs in proportion to infarct size for infarctions involving less 20% of the ventricle. There is little additional hypertrophy in larger infarctions [21]. In rats with infarction of less than 20%, there are minimal, if any changes in haemodynamics or peak pumping capacity of heart. However, rats with large infarctions develop increased left ventricular end diastolic pressures and a rightward shift of left ventricular pressure-volume relation [10]. Progressive left ventricular dilation occurs up to 3 to 4 months post infarction and cardiac output begins to fall at 6 months [15]. Of note, hearts from patients with ischemic cardiomyopathy typically dilated, hypertrophied, and have disproportionately thin walls, suggesting inadequate myocardial thickness for degree of dilatation [19].

IV. Distortion of LV geometry

A. Global shape change

As the heart remodels, its geometry changes: it becomes less elliptical and more spherical. The increased sphericity results from (1) lengthening of the ventricular perimeters, (2) blunting of the normal curvature of the apex, (3) and rounding out of the sharp abnormalities in contour at the margins of the infarct (see below). [22]. Rather than a cause of increased wall stress, increase in global LV sphericity may be viewed as an adaptation to redistribute this abnormal regional wall stress away from the critical border zone of viable myocardium [17].

- ***Sequlae of LV shape changes***

1. LV ejection and filling: natural elliptical shape of the LV has shown to provide best LVEF. This is because the normal systolic motion of the heart includes a twisting action where the apical portion of the LV twists counter-clockwise and basal portion twist clockwise. As ventricle becomes more spherical this twisting ability diminishes reducing both EF and filling [23].
2. Mitral valve orientation: conversion of LV shape into a large sphere induces mitral regurgitation by shifting papillary muscle alignment and by causing annular dilatation [24].
3. Aortic valve orientation: the aortic valve is positioned so that the force vector of the ventricular ejection is directed toward the aortic valve. As the shape of the ventricle becomes distorted, this force vector diminishes, and its direction moves away from the aortic valve. Thus, not only the force of ejections diminished, but also what force remains is misdirected [23].

B. Regional geometrical changes

By performing endocardia curvature analysis of the LV early (2 weeks) after anterior MI, Mitchell et al. showed that at end systole, there was excessive curvature (bulging) of the anterior wall, negative curvature (concavity) at the anterobasal and inferior regions, and diminished curvature

(blunting) of the apex [17]. The peri-infarct zone creates a rim of negative curvature (concavity) encircling the infarct during systole. This produces the subjective appearance of hyperfunction in the infarct zone despite normal or depressed quantitative wall motion. Later on, the global increase of LV volume and sphericity is associated with regional flattening of this zone. The increase of LV sphericity results from rounding out of the sharp contour at this critical zone [17].

V. Wall motion asynergy

Early, the length of the non-contractile segment increase due to the process of infarct expansion. However late after the index infarction, there is decrease of this non contractile segment length. Mitchell et al. reported significant decrease of the non-contractile segment at 1 year follow up compared to the baseline study after anterior MI .This decrease was confined to the akinetic segment, whereas the dyskinetic segment remained unchanged [17].

VI. Other changes

1. Compensatory hyper kinesis of non-infarct area

After large MI, muscle function in the non-infarcted myocardium is augmented initially and then eventually deteriorates without another ischemic insult. It is thought that a mechanical stimulus (i.e., an increase in wall stress) is probably responsible for the progressive deterioration in muscle function [15].

2. Mitral regurgitation

Conversion of LV shape into a large sphere induces mitral regurgitation by shifting papillary muscle positions and by causing annular dilatation [24]. Data from a canine model using 3-D echocardiography suggest functional MR associated with LV dysfunction occurs only in the presence of LV dilatation [25].

3. Diastolic dysfunction

Initially, the left ventricular pressure-volume curve is shifted to the left toward the pressure axis at 24 hours. By 1 week, the curve shifts back away from the pressure axis such that by 3 weeks, the pressure-volume relationship is displaced rightward with large increase in operating end-diastolic volume. The LV continues to dilate with documentation of changes in the pressure-volume relationship up to1 year after infarction [26].

4. Right ventricular remodeling

The data support the contention that post myocardial infarction remodeling is a biventricular process. Hirose et al. studied right ventricular volumes changes during the first year after LV infarction. In patients with anterior MI, there were significant total increases of 13% and 15% in right ventricular EDV and ESV, respectively, by 1 year. Neither EDV nor ESV increased significantly after hospital discharge following inferior wall LV infarction. Similarly, there was a linear relation between LV and right ventricular ejection fractions in patients with anterior MI, but no relation in those with inferior MI [27]. The combined effects of increased volumes due to stretched and dilated infarcted tissue, and the volume and pressure overload in non-infarcted territories leads to the complex entity of post-MI remodeling [28]. Following the initial insult of an acute MI, there ensues a cascade of molecular, cellular and interstitial perturbations which result in characteristic post MI structural remodeling and a subsequent progressive decline in function [29]. Initially, myocardial fibrosis occurs during repair of necrotic tissue with resultant non-contractile scar formation and an elongation and thinning in infarct zone.

An initially adaptive increase in LV blood volumes (and subsequently pressures) follows in an attempt to augment stroke volume and maintain appropriate cardiac output via Starling Mechanism [30]. A gradual progression from an elliptical to a spherical configuration then becomes apparent as hypertrophic myocyte elongation in the non-infarcted zone, known as infarct expansion, leads to an increase in LV mass and an enlargement of the LV cavity [30]. As a result of these changes, the performance of the LV is progressively impaired, exaggerated by loss of function in the pathologically hypertrophied myocytes and interstitial fibrosis with collagen deposition in the extracellular matrix of the non-infarcted zone [31]. Essentially, progression to a more spherical geometry reduces contractile efficiency as cardio-myocytes are required to shorten more to achieve the same ejected net volume [32]. Both the extent of structural LV remodeling and the subsequent reduction in LVEF are directly proportional to the infarct size [33].

3. Left ventricular remodeling and neurohormonal activation

Further to the specific infarct related geometrical changes, progression of LV remodeling is mediated by overexpression of compensatory neurohormonal mechanisms [34]. Sympathetic outflow increased both by attenuated inhibition (baroreceptors and mechanoreceptors) and increased excitation (peripheral chemoreceptors and metaboreceptors) of adrenergic nervous system, such that cardiovascular hemodynamics may be maintained and functional capacity preserved [35]. Renin angiotensin aldosterone system (RAAS) is also activated which, in tandem with increased adrenergic response, facilitates maintenance of cardiac output through sodium and water retention, peripheral arterial vasoconstriction, increased contractility and inflammatory cytokine activation (responsible for cardiac repair) [36]. Ultimately, however, persistent over expression of these and other biologically active compensatory molecules contributes to progression of LV remodeling by virtue of detrimental effect they have on cardiac myocytes and extracellular matrix [37]. To counteract these deleterious effects, counter-regulatory neurohormones such as natriuretic peptides (e.g. B-type natriuretic peptide (BNP), atrial natriuretic peptide (ANP) excreted in an effort to maintain sodium and water homeostasis [38].

4. Prognostic implications of left ventricular remodeling

The development of structural and functional LV remodeling strongly linked to adverse outcome. Death and hospitalization from chronic heart failure (CHF) is closely related to decreasing LVEF and increasing ESV, EDV and infarct length [39]. The specific geometry of LV remodeling is further predictive. For example, it has been reported that those with hypertensive concentric hypertrophy have highest incidence of cardiac events and premature mortality [40]. This, it has been proposed, may be related to prolongation of action potentials, increased dispersion of refractoriness, and lowering of the ventricular fibrillation threshold [41]. Furthermore, independently, and irrespective of etiology,

both LV mass and LV hypertrophy are predictors of cardiovascular morbidity and mortality [42]. This observation extends to a number of pathological contexts. For example, a two to four-fold increase in risk of death or nonfatal complications has been observed where LV hypertrophy exists in conjunction with a diagnosis of hypertension, CAD or uncomplicated MI [43].

5. Assessment of LV Remodeling

Echocardiography and radionuclide ventriculography have provided, to date, the majority of investigational data describing the process of LV remodeling. Recently, magnetic resonance imaging has represented an important addition to the armamentarium of techniques **[44].**

5.1. Measures of LV remodeling: volumes versus ejection fraction

While volumetric LV measurements appear to provide most powerful data regarding process of LV remodeling, estimation of LVEF is simpler to obtain and is indeed a marker of remodeling process. However, it is unlikely that one measurement such as a volume change will provide a complete description in such a biologically complex process [45]. Relative small increases in ventricular volumes are associated with a major independent increase in risk of death of patients with recent MI. While the EDV is a reflection of both structural remodeling and diastolic filling, ESV remains most powerful predictor of survival after AMI. Progressive increment of only 25 ml in ESV increased relative risk of death in an exponential manner [46]. However, ESV influenced by both EDV and fiber shortening, and asymmetric contraction may make echocardiographically derived measures of ESV inaccurate [47].

6. Therapeutic Intervention and Reversal of LV Remodeling

During acute phase, limiting the infarct size is highly desirable. This is achieved by reperfusion therapy. Beyond the acute phase, several classes of drugs have been shown to have a major impact on LV remodeling, most likely through a combination of load-related and non-load-related mechanisms. Each of these drug classes has been shown to reduce morbidity and mortality [44].

I. Reperfusion therapy

Fibrinolytic agents or PCI would provide benefit at two phases:

1) In early reperfusion, only a thin endocardial rim of myocardium would be infracted, resulting in the ultimate return of regional function.
2) In late reperfusion, it may promote scar healing, prevent apoptosis, and support remaining viable myocytes [48].

II. Medical therapy

1. ACE inhibitors have been shown to prevent post infarction progressive increase in EDV and ESV observed in placebo-treated groups. This effect noticed in several trials performed in both asymptomatic and symptomatic patients [49]. The mechanisms of beneficial effects of ACE inhibitors on remodeling include:

- Reduction of circulating ACE activity.
- Reduction of tissue ACE and myocyte and fibroblast growth factors
- Reduction of ischemic or reperfusion injury and of infarct size.
- Improvement of haemodynamics and decreased wall stress.
- Improvement in collateral blood flow (bradykinin-mediated) [50].

2. Beta blockers have been shown to have a major impact on the remodeling process. These agents exerts their salutary effects on remodeling through modulation of direct adrenergic effects on the myocardium, reduction of myocardial ischemia and prevention of recurrent MI, and by reduction of heart rate [51].

3. Angiotensin receptor blockers (ARBs) have been shown to reduce ventricular volumes in patients with heart failure and baseline ventricular dilatation, an effect most prominent in patients not receiving maximal background therapy with ACE inhibitors and beta blockers [52].

4. Aldosterone receptor blockers also reverse LV remodeling following MI [53] and in patients with heart failure [54].

III. Biventricular pacing (cardiac resynchronization therapy)

Beneficial influence of cardiac resynchronization therapy on LV remodeling has received much attention. In Sync Randomized Clinical Evaluation (MIRACLE) trial, there was a decrease in LV size (3.5 mm decrease in internal diastolic dimension) and an increase in LVEF [55].

IV. Surgical approaches

There have many surgical attempts to reverse LV remodeling. One is partial left ventriculectomy, or Batista operation. In this operation, a portion of LV free wall b/w papillary muscles excised in combination with mitral valve surgery. But, Results of this surgery were disappointing [56].

References

[1] J.M. Pfeffer, M.A. Pfeffer, P.J. Fletcher, E. Braunwald. (1991). Progressive ventricular remodeling in rat with myocardial infarction. American Journal of Physiology-Heart and Circulatory Physiology. 260(5): H1406-H1414.

[2] P.M. Pilz, J.E. Ward, W.-T. Chang, A. Kiss, E. Bateh, A. Jha, S. Fisch, B.K. Podesser, R. Liao. (2022). Large and small animal models of heart failure with reduced ejection fraction. Circulation research. 130(12): 1888-1905.

[3] W. Krueger, N. Bender, M. Haeusler, M. Henneberg. (2021). The role of mechanotransduction in heart failure pathobiology—a concise review. Heart failure reviews. 26(4): 981-995.

[4] E. Bontaş, F. Radu-Ioniţă, L. Stan. (2018). Hypertrophy and Dilatation, Markers of Dysfunction. Right Heart Pathology: From Mechanism to Management. 179-201.

[5] M.G.S.J. Sutton, N. Sharpe. (2000). Left ventricular remodeling after myocardial infarction: pathophysiology and therapy. Circulation. 101(25): 2981-2988.

[6] G.M. Hutchins, B.H. Bulkley. (1978). Infarct expansion versus extension: two different complications of acute myocardial infarction. The American journal of cardiology. 41(7): 1127-1132.

[7] H.F. Weisman, D.E. Bush, J.A. Mannisi, M.L. Weisfeldt, B. Healy. (1988). Cellular mechanisms of myocardial infarct expansion. Circulation. 78(1): 186-201.

[8] M.A. Pfeffer. (1998). ACE inhibitors in acute myocardial infarction: patient selection and timing. Circulation. 97(22): 2192-2194.

[9] L.W. Eaton, J.L. Weiss, B.H. Bulkley, J.B. Garrison, M.L. Weisfeldt. (1979). Regional cardiac dilatation after acute myocardial infarction: recognition by two-dimensional echocardiography. New England Journal of Medicine. 300(2): 57-62.

[10] M.H. Picard, G.T. Wilkins, L.D. Gillam, J.D. Thomas, A.E. Weyman. (1991). Immediate regional endocardial surface expansion following coronary occlusion in the canine left ventricle: disproportionate effects of anterior versus inferior ischemia. American heart journal. 121(3): 753-762.

[11] E.H. Schuster, B.H. Bulkley. (1979). Expansion of transmural myocardial infarction: a pathophysiologic factor in cardiac rupture. Circulation. 60(7): 1532-1538.

[12] J.L. Meizlish, H.J. Berger, M. Plankey, D. Errico, W. Levy, B.L. Zaret. (1984). Functional left ventricular aneurysm formation after acute anterior transmural myocardial infarction: incidence, natural history, and prognostic implications. New England Journal of Medicine. 311(16): 1001-1006.

[13] M. St John Sutton, M. Pfeffer, T. Plappert, J. Rouleau, L. Moye, G. Dagenais, G. Lamas, M. Klein, B. Sussex, S. Goldman. (1994). Quantitative two-dimensional echocardiographic measurements are major predictors of adverse cardiovascular events after acute myocardial infarction. The protective effects of captopril. Circulation. 89(1): 68-75.

[14] R.W. Jeremy, K.C. Allman, G. Bautovitch, P.J. Harris. (1989). Patterns of left ventricular dilation during the six months after myocardial infarction. Journal of the American College of Cardiology. 13(2): 304-310.

[15] M.A. Gaballa, S. Goldman. (2002). Ventricular remodeling in heart failure. Journal of cardiac failure. 8(6): S476-S485.

[16] G. Mitchell, G. Lamas, D. Vaughan, M. Pfeffer. (1989). Infarct expansion does not contribute to late left ventricular enlargement. Circulation. 80(suppl II): II-589.

[17] M. GF. (1992). Left ventricular remodeling in the year after first anterior myocardial infarction: A quantitative analysis of cantractile segment lengths and ventricular shape. J Am Coll Cardiol. 19: 1136-1144.

[18] A.M. Gerdes. (2002). Cardiac myocyte remodeling in hypertrophy and progression to failure. Journal of cardiac failure. 8(6): S264-S268.

[19] A.M. Gerdes, S.E. Kellerman, J.A. Moore, K.E. Muffly, L.C. Clark, P.Y. Reaves, K.B. Malec, P.P. McKeown, D.D. Schocken. (1992). Structural remodeling of cardiac myocytes in patients with ischemic cardiomyopathy. Circulation. 86(2): 426-430.

[20] J.-i. Sadoshima, L. Jahn, T. Takahashi, T.J. Kulik, S. Izumo. (1992). Molecular characterization of the stretch-induced adaptation of cultured cardiac cells. An in vitro model of load-induced cardiac hypertrophy. Journal of Biological Chemistry. 267(15): 10551-10560.

[21] S.A. Rubin, M.C. Fishbein, H. Swan, A. Rabines. (1983). Compensatory hypertrophy in the heart after myocardial infarction in the rat. Journal of the American College of Cardiology. 1(6): 1435-1441.

[22] B. Swynghedauw. (1999). Molecular mechanisms of myocardial remodeling. Physiological reviews. 79(1): 215-262.

[23] H. Azhari, R. Beyar, S. Sideman. (1999). On the human left ventricular shape. Computers and biomedical research. 32(3): 264-282.

[24] B.A. Carabello, Ischemic mitral regurgitation and ventricular remodeling. In American College of Cardiology Foundation Washington, DC: 2004; Vol. 43, pp 384-385.

[25] Y. Otsuji, M.D. Handschumacher, E. Schwammenthal, L. Jiang, J.-K. Song, J.L. Guerrero, G.J. Vlahakes, R.A. Levine. (1997). Insights from three-dimensional echocardiography into the mechanism of functional mitral regurgitation: direct in vivo demonstration of altered leaflet tethering geometry. Circulation. 96(6): 1999-2008.

[26] T.E. Raya, R.G. Gay, L. Lancaster, M. Aguirre, C. Moffett, S. Goldman. (1988). Serial changes in left ventricular relaxation and chamber stiffness after large myocardial infarction in rats. Circulation. 77(6): 1424-1431.

[27] K. Hirose, N.H. Shu, J.E. Reed, J.A. Rumberger. (1993). Right ventricular dilatation and remodeling the first year after an initial transmural wall left ventricular myocardial infarction. The American journal of cardiology. 72(15): 1126-1130.

[28] S.A. Leancă, D. Crișu, A.O. Petriș, I. Afrăsânie, A. Genes, A.D. Costache, D.N. Tesloianu, I.I. Costache. (2022). Left ventricular remodeling after myocardial infarction: from physiopathology to treatment. Life. 12(8): 1111.

[29] S.D. Prabhu, N.G. Frangogiannis. (2016). The biological basis for cardiac repair after myocardial infarction: from inflammation to fibrosis. Circulation research. 119(1): 91-112.

[30] L. Zhang, T. Li, Y. Yu, K. Shi, Z. Bei, Y. Qian, Z. Qian. (2023). An injectable conductive hydrogel restores electrical transmission at myocardial infarct site to preserve cardiac function and enhance repair. Bioactive Materials. 20: 339-354.

[31] W.J. Paulus, M.R. Zile. (2021). From systemic inflammation to myocardial fibrosis: the heart failure with preserved ejection fraction paradigm revisited. Circulation research. 128(10): 1451-1467.

[32] J.G. Travers, C.A. Tharp, M. Rubino, T.A. McKinsey. (2022). Therapeutic targets for cardiac fibrosis: from old school to next-gen. The Journal of clinical investigation. 132(5).

[33] B. Ibanez, A.H. Aletras, A.E. Arai, H. Arheden, J. Bax, C. Berry, C. Bucciarelli-Ducci, P. Croisille, E. Dall'Armellina, R. Dharmakumar. (2019). Cardiac

MRI endpoints in myocardial infarction experimental and clinical trials: JACC scientific expert panel. Journal of the American College of Cardiology. 74(2): 238-256.

[34] G. Jia, M.A. Hill, J.R. Sowers. (2018). Diabetic cardiomyopathy: an update of mechanisms contributing to this clinical entity. Circulation research. 122(4): 624-638.

[35] M.a. Hanson, P. Gluckman. (2014). Early developmental conditioning of later health and disease: physiology or pathophysiology? Physiological reviews. 94(4): 1027-1076.

[36] G.D. Flora, M.K. Nayak. (2019). A brief review of cardiovascular diseases, associated risk factors and current treatment regimes. Current pharmaceutical design. 25(38): 4063-4084.

[37] S. Gallo, A. Vitacolonna, A. Bonzano, P. Comoglio, T. Crepaldi. (2019). ERK: a key player in the pathophysiology of cardiac hypertrophy. International journal of molecular sciences. 20(9): 2164.

[38] N. Ghionzoli, F. Gentile, A.M. Del Franco, V. Castiglione, A. Aimo, A. Giannoni, S. Burchielli, M. Cameli, M. Emdin, G. Vergaro. (2022). Current and emerging drug targets in heart failure treatment. Heart failure reviews. 27(4): 1119-1136.

[39] L. Nepper-Christensen, J. Lønborg, K.A. Ahtarovski, D.E. Høfsten, K. Kyhl, A.A. Ghotbi, M.M. Schoos, C. Göransson, L. Bertelsen, L. Køber. (2017). Left ventricular hypertrophy is associated with increased infarct size and decreased myocardial salvage in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. Journal of the American Heart Association. 6(1): e004823.

[40] M. Yildiz, A.A. Oktay, M.H. Stewart, R.V. Milani, H.O. Ventura, C.J. Lavie. (2020). Left ventricular hypertrophy and hypertension. Progress in cardiovascular diseases. 63(1): 10-21.

[41] V. András, J. Tomek, N. Nagy, L. Virág, E. Passini, B. Rodriguez, I. Baczkó. (2021). Cardiac transmembrane ion channels and action potentials: cellular physiology and arrhythmogenic behavior. Physiological reviews.

[42] C.N. Bang, E.Z. Soliman, L.M. Simpson, B.R. Davis, R.B. Devereux, P.M. Okin, f.t.A.C.R. Group. (2017). Electrocardiographic left ventricular hypertrophy predicts cardiovascular morbidity and mortality in hypertensive patients: the ALLHAT study. American journal of hypertension. 30(9): 914-922.

[43] G. Mancia Chairperson, M. Brunström, M. Burnier, G. Grassi, A. Januszewicz, M. Muiesan, K. Tsioufis, E. Agabiti-Rosei, A. Eae, M. Azizi. (2023). 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension Endorsed by the European Renal Association (ERA) and the International Society of Hypertension (ISH). Journal of hypertension. 41(12): 1874-2071.

[44] M.A. Konstam, J.E. Udelson, N. Sharpe. (2002). Prevention and reversal of left ventricular remodeling: summation. Journal of cardiac failure. 8(6): S506-S511.

[45] J.E. Udelson, M.A. Konstam. (2002). Relation between left ventricular remodeling and clinical outcomes in heart failure patients with left ventricular systolic dysfunction. Journal of cardiac failure. 8(6): S465-S471.

[46] H.D. White, R.M. Norris, M.A. Brown, P.W. Brandt, R. Whitlock, C.J. Wild. (1987). Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. Circulation. 76(1): 44-51.

[47] C. JN. (2000). Cardiac remodeling: Concepts and clinical implications: A consensus paper from an international forum on cardiac remodelling. J Am Coll Cardiol. 35: 269-282.

[48] D.A. Touchstone, G.A. Beller, T.W. Nygaard, C. Tedesco, S. Kaul. (1989). Effects of successful intravenous reperfusion therapy on regional myocardial function and geometry in humans: a tomographic assessment using two-dimensional echocardiography. Journal of the American College of Cardiology. 13(7): 1506-1513.

[49] A.W. Stanley, C.L. Athanasuleas, G.D. Buckberg, R. Group. (2005). Heart failure following anterior myocardial infarction: an indication for ventricular restoration, a surgical method to reverse post-infarction remodeling. Heart failure reviews. 9: 241-254.

[50] B.I. Jugdutt, M.I. Khan, S.J. Jugdutt, G.E. Blinston. (1995). Effect of enalapril on ventricular remodeling and function during healing after anterior myocardial infarction in the dog. Circulation. 91(3): 802-812.

[51] C. Ceconi, A. Boraso, R. Ferrari. (2002). Future strategies of reverse remodeling prevention of hibernation. Journal of cardiac failure. 8(6): S542-S548.

[52] C. JN. (2001). Valsartan heart failure trial investigators: a randomized trial of the angiotensin-receptor blocker valsasrtan in chronic heart failure. N Engl J Med. 345: 1667-1675.

[53] T. Tsutamoto, A. Wada, K. Maeda, N. Mabuchi, M. Hayashi, T. Tsutsui, M. Ohnishi, M. Sawaki, M. Fujii, T. Matsumoto. (2001). Effect of spironolactone on plasma brain natriuretic peptide and left ventricular remodeling in patients with congestive heart failure. Journal of the American College of Cardiology. 37(5): 1228-1233.

[54] M. Hayashi, T. Tsutamoto, A. Wada, T. Tsutsui, C. Ishii, K. Ohno, M. Fujii, A. Taniguchi, T. Hamatani, Y. Nozato. (2003). Immediate administration of mineralocorticoid receptor antagonist spironolactone prevents post-infarct left ventricular remodeling associated with suppression of a marker of myocardial collagen synthesis in patients with first anterior acute myocardial infarction. Circulation. 107(20): 2559-2565.

[55] A. Wt. (2002). Cardiac resynchronization in chronic heart failure. N Engl J Med. 346: 1845-1853.

[56] J.P. Boehmer. (2003). Device therapy for heart failure. The American journal of cardiology. 91(6): 53-59.