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MYOCARDIAL DISEASE (A ABBATE, SECTION EDITOR)

Adverse Remodeling and Reverse Remodeling After Myocardial Infarction

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Abstract
Purpose of Review The purpose of this review it to summarize the current literature on remodeling after myocardial infarction, inclusive of pathophysiological considerations, imaging modalities, treatment strategies, and future directions.
Recent Findings As patients continue to live longer after myocardial infarction (MI), the prevalence of post-MI heart failure continues to rise. Changes in the left ventricle (LV) after MI involve complex interactions between cellular and extracellular components, under neurohormonal regulation. Treatments to prevent adverse LV remodeling and promote reverse remodeling in the post-MI setting include early revascularization, pharmacotherapy aimed at neurohormonal blockade, and device-based therapies that address ventricular dyssynchrony.
Summary Despite varying definitions of adverse LV remodeling examined across multiple imaging modalities, the presence of an enlarged LV cavity and/or reduced ejection fraction is consistently associated with poor clinical outcomes. Advances in our knowledge of the neurohormonal regulation of adverse cardiac remodeling have been instrumental in generating therapies aimed at arresting adverse remodeling and promoting reserve remodeling. Further investigation into other specific mechanisms of adverse LV remodeling and pathways to disrupt these mechanisms is ongoing and may provide incremental benefit to current evidence-based therapies.

Keywords Remodeling · Myocardial infarction · Left ventricle · Heart failure · Ischemic cardiomyopathy

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Introduction

Heart failure (HF) is a leading cause of morbidity and mortality worldwide. Recent projections show that the prevalence of HF will increase from approximately six million to more than eight million patients by 2030 [1]. Coronary artery disease (CAD) is the major pathophysiological driver of myocardial infarction (MI) and the number 1 cause of HF in the USA. A recent NHANES survey found that the development of CAD conferred a relative risk of HF of 8.1, over fourfold larger than the relative risk of HF from other major risk factors including cigarette smoking, hypertension, obesity, and diabetes mellitus [2].

As more patients survive and live longer after MI, the incidence and prevalence of post-MI HF continue to rise. The development of the HF phenotype in these patients arises from a complex, progressive, molecular, and cellular transformation called "ventricular remodeling." First described by Tennant and Wiggers, ventricular remodeling includes dilatation of the ventricle, the formation of scar, and geometrical changes in the overall left ventricle (LV) shape (i.e., ellipsoid to more spherical) and is driven, in part, by neurohormonal pathways) [3]. Major evidenced-based HF therapies target these neurohormonal pathways in attempts to prevent adverse remodeling and promote reverse remodeling, aimed ultimately at improving outcomes in the post-MI population.

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In this review, we aim to (1) define the molecular, cellular, and imaging features that define adverse cardiac remodeling; (2) summarize the current literature on pharmacotherapy and device-based therapies to prevent adverse remodeling and promote reverse remodeling; and (3) discuss areas of ongoing investigation and future research.

Mechanisms of Adverse Cardiac Remodeling

Early Cellular Changes

Remodeling begins with an acute infarct, leading to myocardial injury and death, but involves a progressive group of changes that occur in both infarcted and non-infarcted myocardia (Fig. 1**)**. Early changes can be seen within hours to days of an acute myocardial insult. Myocardial necrosis results in an influx of inflammatory cells, including macrophages and other antigen-presenting cells [4]. These processes occur early, about days 3–4, in the development of an acute MI. The influx of these inflammatory cells leads to the destruction of the collagen scaffolding that helps to maintain ventricular shape [5], leading to regional thinning and dilation of the myocardium in the infarcted areas [6]. During this period, fibroblasts are also directed to the site of myocardial injury and begin to deposit new a collagen matrix that contributes to scar formation in the immediate post-infarct period.

Late Cellular Changes

Over the following weeks to months, the viable myocardium undergoes a series of changes. Principally, given increased load on the non-infarcted myocardium, myocytes undergo eccentric hypertrophy, further leading to LV cavity dilation [7, 8]. These processes are initially compensatory and aimed at preserving cardiac output in response to infarcted myocardium and the resulting non-compliant scar formation. Over time, these changes increase LV size, which causes increasing wall stress and further dilation. These processes lead to increases in LV end-systolic and end-diastolic volumes, increase preload-dependent myocardial oxygen demand, and may ultimately promote increased areas at risk for ischemia [9]. Progressive dilatation leads to further hemodynamic consequences, including the formation of possibly both ischemic and functional mitral regurgitations, which have been previously reviewed [10]. As LV preload increases without the subsequent ability to generate sufficient myocardial contractility due to the thinning of the myocardial wall, end-systolic volumes rise and result in a depression of LV ejection fraction (EF). These processes are central to the development of ischemia-driven dilated cardiomyopathy.

Extracellular Matrix Changes

The extracellular matrix (ECM) surrounds cardiac myocytes and is responsible for the formation of a cellular scaffold that maintains the LV shape and geometry. Within the ECM arises a complex interaction between cellular components, such as fibroblasts, in addition to collagen, matrix metalloproteinases (MMP), and cell surface adhesion molecules. The ECM is actively turned over during adverse cardiac remodeling through the balance of MMP and their inhibitors (tissue inhibitors of metalloproteinases (TIMPs)). In animal models of MI, after coronary artery ligation, levels of collagenase and MMPs rose sharply at day 2 and peaked by day 7. In this same study, the expression of TIMPs also rose sharply after infarction, peaking at day 2 [5]. Similar results were seen in a small trial of post-MI patients compared to age-matched controls [11]. The regulation of MMPs and TIMPs is coordinated at both the transcriptional and translational levels through a myriad of

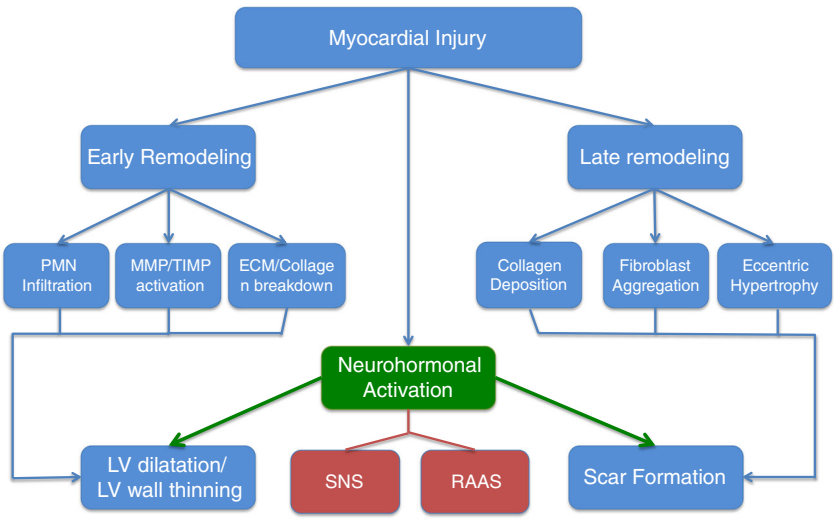

Fig. 1 Major interactions between cellular, extracellular, and neurohormonal components in the development of adverse post-MI cardiac remodeling

transcription factors and enzymes, including the NF-κB and JAK-STAT pathways. Importantly, regulation of these pathways may be influenced by the neurohoromonal activation principally the activation of the renin-angiotensin-aldosterone system (RAAS). Angiotensin II activates transcription factors, leading to the production of type I collagen, and activates antiapoptotic factors that may drive hypertrophy [12]. Thus, ventricular remodeling results from a complex interaction between cellular changes and transformation of the extracellular matrix under direct neurohormonal control.

Neurohormal Regulation

Neurohormones serve as critical regulatory pathways for the development of adverse cardiac remodeling and thereby serve as pharmacological targets for the prevention of prevent adverse remodeling and promote reverse remodeling. Specifically, the major cardioregulatory hormonal cascades implicated in LV remodeling include the sympathetic nervous system (SNS) and the RAAS [13].

The SNS provides β-adrenergic tone, aimed at increasing heart rate and stroke volume. While these measures may be compensatory in the acute decompensated state, persistent sympathetic activation can cause deleterious effects on the LV. In transgenic mouse models, overexpression of the β1-A receptor leads initially to augmented cardiac output, but sustained expression leads to LV hypertrophy and HF [14]. Specifically, sustained SNS overactivity can impair excitation-contraction coupling [15] and enhance apoptotic pathways [16]. In addition, chronic catecholamine activity may independently reduce cardiac function, promote fibrosis, and induce oxidative damage [17]. Finally, chronic SNS activation is a critical promoter of RAAS activation, thereby mediating the adverse effects of angiotensin II.

The RAAS is also critical to the promotion of adverse cardiac remodeling. After coronary ligation in rats, angiotensinogen was significantly elevated in the non-infarcted portion of the LV by 5 days post-infarction [18]. Much of the effect of RAAS on adverse cardiac remodeling may stem from increased angiotensin II expression. In rat models, sustained infusion of angiotensin II leads to increases in perivascular and interstitial collagen content [19]. Angiotensin II also has a direct cytotoxic effect on cardiac myocytes, leading to acceleration of apoptosis and promotion of cell hypertrophy. Interestingly, the predominant interaction thought to promote adverse cardiac remodeling has been found to be via binding of angiotensin II to the angiotensin II type 1 receptor (AT-1R). For example, a greater density of AT-1R on circulating platelets may confer and increased likelihood for prolonged adverse ventricular remodeling [20]. In fact, angiotensin II signaling through AT-2R is thought to be a counteregulatory interaction that promotes cardioprotective effects, leading to interests in developing biased ligands as potential therapeutic targets [21].

Cardiac Imaging of Adverse Cardiac Remodeling

Major cardiology societies have routinely recommended obtaining a complete chest wall transthoracic echocardiogram (TTE) within the first 24–48 h after MI [22, 23]. Evidence of adverse cardiac remodeling can often be readily seen on TTE even in the early stages of infarction. In addition, other imaging modalities that allow more precise tissue characterization (i.e., cardiac magnetic resonance imaging) have also begun to gain prevalence in the post-MI population.

Several studies have sought to describe LV changes that may portend adverse clinical outcomes using varying imaging modalities. In early clinical studies, White et al. assessed LV parameters using contrast venticulography 4–8 weeks post-infarction on 605 patients with a mean follow-up period of 78 months and found that end-systolic volume (ESV) had greater predictive value for survival than end-diastolic volume (EDV) or ejection fraction (EF) [24]. Similarly, Migrino et al. found LVESV index assessed by ventriculography 90–180 min after thrombolysis to be a strong predictor of 6-month mortality [25].

Volume assessments by TTE have also been shown to correlate to clinical outcomes. A study of 284 MI patients receiving PCI found that adverse remodeling (defined as >20% EDV increase) increased the risk for long-term mortality with a mean follow-up period of 60 months, though the pattern of LV dilation and the time course in which it occurred did not differentially affect event rates [26]. Similarly, Lee et al. found that LV end-diastolic index by M-mode echocardiography predicted all-cause mortality independent of EF in a chronic HF cohort [27]. In the echocardiogram substudy of the VALIANT trial, larger infarct size and decreases in LVEF were predictive of all-cause mortality and LVESV and LVEDV correlated with clinical events [28] (Fig. 2a, b). Another VALIANT substudy found that abnormal LV geometry (measured by LV mass index and relative wall thickness [RWT]) increased the risk of major cardiac events as compared to those patients with normal geometry [29]. Interval changes in LV dimensions as assessed by TTE have also been found to correlate with clinical outcomes. The echocardiographic substudy of the SAVE clinical trial found that irrespective of treatment assignment, greater increases in LV systolic area from baseline (mean 11 days post-MI) to 1 year correlated with adverse clinical outcomes [30]. Similar results were seen in the chronic HF trial Val-HeFT [31]. In aggregate, these studies suggest that despite the heterogeneity in the definition of LV remodeling by TTE, evidence of larger LV volumes has consistently been shown to result in poor clinical outcomes.

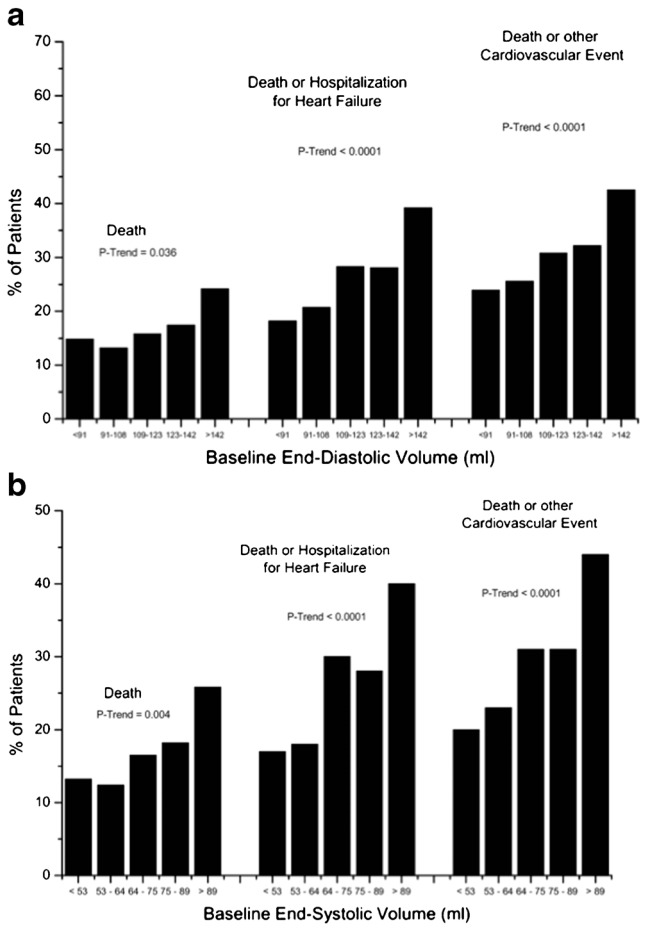

Fig. 2 **a** Relationship between baseline end-diastolic volumes and total mortality, death, or hospitalization for heart failure and death or other cardiovascular event (heart failure, MI, stroke, resuscitated sudden death) from the VALIANT randomized clinical trial (adapted from Solomon et al. [28]. **b** Relationship between end-systolic volume and total mortality, death, or hospitalization for heart failure and death or other cardiovascular events (heart failure, MI, stroke, resuscitated sudden death) from the VALIANT randomized clinical trial (adapted from Solomon et al.) [28]

The emergence of cardiac magnetic resonance imaging (CMR) may provide additional relevant information with regard to ventricular remodeling. CMR is more precise method for the evaluation of LV mass and volume with reduced inter-reader variability as compared to TTE [32]. In addition, via the technique of late gadolinium enhancement (LGE), CMR has the ability to determine infarct age and distinguish between reversible versus irreversible myocardial injury [33•, 34], though the clinical significance of determining myocardium at-risk is still controversial. CMR may also provide more precise information with regard to scar formation and location, the nature of transmural necrosis, and microvascular obstruction, which have been shown to be predictors of LV dilatation and adverse cardiac remodeling [35].

Despite strong evidence of the correlation between LV parameters and clinical outcomes, the relationship with remodeling and functional outcomes has been incompletely studied. Studies have shown impairments in quality of life and functional status after MI as compared to age-matched controls [36]. A study of 256 MI patients demonstrated that reduced EF by TTE on index hospitalization was a strong correlate for the worse health-related quality of life outcomes as measured by the Kansas City Cardiomyopathy Questionnaire and the EuroQol-5 dimensions [37], though ventricular volumes have not been correlated to functional outcomes in a post-MI cohort.

Overall, the clinical assessment of LV remodeling is heterogeneous and poorly defined. While the use of echocardiography has been a traditional way to assess LVEF and LV volumes, other methods do exist and head-to-head comparisons are limited. Despite varied definitions of adverse LV remodeling, imaging findings suggestive of a dilated LV cavity and/or a reduced EF are associated with a poor long-term prognosis, and may represent delayed reperfusion and/or larger infarct size.

Preventing Adverse Remodeling and Promoting Reverse Remodeling

Therapeutic interventions have been incrementally developed to reduce infarct size and to interfere with neurohoromonal activation which is central to the development and progression of adverse cardiac remodeling and ultimately improve clinical outcomes. Therapeutic interventions include, but are not limited to, early revascularization and infarct artery patency, pharmacological targets, and device-based approaches (Fig. 3).

Thrombolysis and Revascularization

Early revascularization has been shown to improve outcomes in post-MI patients. Early revascularization may also be beneficial in limiting infarct size and progressive LV dysfunction. Early studies of thrombolysis showed that early (<4 h from symptom onset) intervention with thrombolytic therapy limited the extent of LV wall motion abnormalities [38]. In a randomized clinical trial assessing changes in ventricular volumes (by TTE) 6 months after MI, patients treated with streptokinase experienced smaller LVESV and LVEDV, despite no changes in EF, as compared to patients medically treated without streptokinase [39]. Infarct artery patency may also be an important marker for long-term outcomes [40, 41]. Patients post-percutaneous coronary intervention (PCI) that experience <TIMI 2 flow had worse clinical outcomes than those experiencing TIMI 3 flow with primary PCI [42]. Given the importance of infarct artery patency, other chronic CAD therapies (i.e., statins, antiplatelet agents, etc.) may be important mediators of remodeling, though this has not been empirically studied.

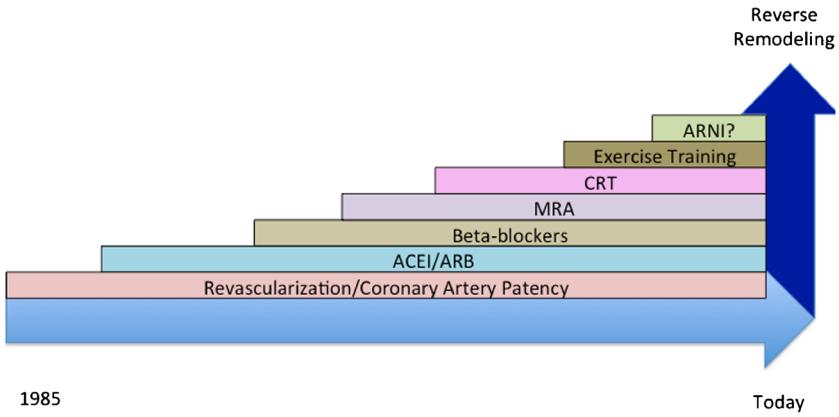

Fig. 3 Major therapeutic advances to stop adverse LV remodeling and promote reverse remodeling in patients after myocardial infarction. *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *ARNI* angiotensin receptor-neprilysin inhibitor, *CRT* cardiac resynchronization therapy, *MRA* mineralocorticoid receptor antagonists

Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers

As previously highlighted, the RAAS, and particularly angiotensin II, has been implicated in the regulation and progression of pathways that promote adverse cardiac remodeling. Angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blockers (ARBs) have consistently shown a survival benefit in the post-MI population. Early trials of patients treated with thrombolytic therapy showed ACEI initiated early post-MI was associated with improved short-term mortality, which persisted at 12 months post-MI [43, 44]. The SAVE trial found large reductions in the mortality and morbidity in the captopril group after MI [45]. Similar results were seen with the ACEI ramipril, given 2–8 days after acute MI, with improvements in all-cause death apparent as early as 30 days post-MI [46]

These improvements in mortality may be partially mediated by the effects of these drugs on LV remodeling. Initial studies found that captopril administration after acute MI resulted in reductions in LVEDV and LV filling pressures and improvement in exercise capacity as compared to patients not treated [47]. The echocardiographic substudy showed smaller LVED and LVES areas in the captopril group compared to placebo [30].

Administration of ARBs showed similar improvements in clinical outcomes to ACEI post-MI. The OPTIMMAL clinical trial of 5770 patients compared the efficacy of captopril (50 mg three times daily) to losartan (50 mg once daily) in the post-MI population. Findings included statistically equivalent efficacy in terms of all-cause mortality, though there was a trend toward improved outcomes in the captopril group [48]. The VALIANT trial of over 14,000 patients found no differences in efficacy between valsartan and captopril in patients with MI who began treatment within 10 days over a median of 24.7 months [49].

The effect of ARBs specifically on LV remodeling has been studied in smaller substudies of larger mortality trials. The echocardiographic substudy of VALIANT found that valsartan, captopril, or both resulted in similar improvements in EF and infarct segment length from baseline through 20 months after MI [28]. In the Val-HeFT trial, which recruited ambulatory HF patients irrespective of etiology (i.e., ischemic vs. non-ischemic), patients treated with valsartan had reductions in LV internal dimension in diastole and increased improvement in LVEF across all time points as compared to those treated with placebo. Interestingly, patients with baseline largest LV internal dimension in diastole and lowest EF experienced the greatest benefit [23].

Overall, ACEI/ARBs have been well-established in the post-MI population in terms of mortality reduction, and have been shown to slow adverse modeling as compared to placebo.

β-Blockers

Excess sympathetic tone is hypothesized to be a major driver of adverse cardiac remodeling via regulation of transcription/translation and activation of other hormonal pathways, including the RAAS. β-Blockers have consistently been shown to provide a survival advantage in HF [50, 51]. Particularly in the post-MI population with known LV dysfunction, the relative risk reduction with carvedilol on all-cause mortality was 23% as compared to placebo. This beneficial effect was seen in addition to ACEIs, which were highly utilized in both the carvedilol and placebo groups [52]. In the same trial, patients treated with carvedilol also had evidence of slowed adverse remodeling, with smaller increases in LVESV and higher LVEF at 6 months post-MI as compared to controls [53]. In an ambulatory HF population, improvements in LVEF with carvedilol were dose-dependent [54]. Studies with bisoprolol showed that intravenous administration resulted in improvements in stroke volume and decreased wall stress only when given to rats with large infarct sizes, suggesting a central role in beta-adrenergic blockade in infarct remodeling [55]. β-Blocker therapy in post-MI patients has been consistently shown to improve clinical outcomes and alter the geometry of the heart in the HF phenotype. While difficult to empirically

evaluate, a portion of the survival advantage may be secondary to the slowing of adverse LV remodeling.

Mineralocorticoid Receptor Antagonists

Mineralocorticoid receptor antagonists (MRAs) are thought to be central molecules in the regulation of the ECM, particularly in the deposition of collagen into the myocardium. The effect of a MRA on survival in the post-MI population was studied in the EPHESUS study, which showed a relative risk reduction in all-cause mortality of 15% with the use of the MRA eplerenone in post-MI patients with a reduced EF and either signs/symptoms of HF or diabetes mellitus. Again, the benefits of MRAs were seen in addition to the background therapy including ACEIs/ARBs and β-blockers [56].

The evidence for MRA with respect to LV remodeling is more limited; in a chronic HF trial with about 60% of patients with an ischemic etiology of HF, treatments with eplerenone did not result in significant changes in LVESV or LVEDV index at 36 weeks as compared to placebo, but did show reductions in collagen turnover in the eplerenone group. Of note, a follow-up study of EPHESUS found that higher type I collagen telopeptide levels correlated with increased rates of all-cause mortality and the composite of CV mortality/HF hospitalization. Levels of the pro-peptide of type I and type III procollagen were found to be consistently lower in the eplerenone group, suggesting that MRA suppressed post-MI collagen turnover [57].

Cardiac Resynchronization Therapy

In patients with severe HF, reduced EF, and electrocardiographic evidence of ventricular dyssynchrony, cardiac resynchronization therapy (CRT) has been shown to improve survival [58], HF events [59], symptoms, and quality of life [60, 61]. Subanalyses from major CRT clinical trials found CRT to be associated with significant improvements in LVESV index [62]. Rates of death and hospitalization were significantly lower in patients in whom CRT led to above median improvements in LVESV and left atrial volume [63••]. Similarly, risk of ventricular arrhythmias was lowest in patients who attained ≥25% reductions in LVESV at 1 year with CRT. No single echocardiographic measure of dyssynchrony has been shown to improve selection of patients that may have greatest beneficial response to CRT and up to 30–35% of patients may be non-responders to CRT based on the current indications [64]. In addition, CRT may not be beneficial in all ischemic cardiomyopathy patients; a recent analysis found that the extent of viable myocardium by gated SPECT was directly proportional to CRT response [65]. Overall, CRT has been shown to be a powerful tool in reverse modeling, and high responders to CRT also exhibit fewer clinical events, though optimal patient selection continues to remain a clinical challenge.

Cardiac Rehabilitation

Exercise training has been shown to reduce sympathetic outflow, circulating catecholamines, angiotensin II, vasopressin, and brain natriuretic peptides, and therefore may be beneficial with respect to cardiac remodeling [66]. In rat models of HF induced with overdrive pacing, exercise training reduced sympathetic tone and angiotensin levels [67]. A small study of 19 HF patients found that exercise training (walking 3× a week for 16 weeks) led to significant reductions in angiotensin, aldosterone, and vasopressin at 16 weeks [68]. Contemporary evidence on the role of exercise training on outcomes post-MI has been conflicting. A multicenter trial of 1813 patients found a comprehensive cardiac rehabilitation program to have no effect on mortality, CV morbidity, or health-related quality of life at 12–24 months [69]. The HF-ACTION trial of a structured exercise intervention in stable outpatients with HF with a reduced EF found aerobic exercise to be safe and led to modest improvements in disease-specific and generic health status and functional capacity [70, 71].

The impact of exercise training on LV remodeling may in part be determined by the type of exercise undertaken. Aerobic interval training was found to have greater reductions in LVESV and LVEDV and greater improvements in LVEF as compared to moderate continuous training for 12 weeks in one study [72], though more recent evidence suggests that high-intensity interval training was not superior to moderate-intensity training in terms of improvements in LVED diameter [73]. Similar results in terms of improvements with aerobic interval training were seen in a meta-analysis of 812 HF patients enrolled across 14 clinical trials [74]. A 2-month training program consisting of two 1-h sessions of walking daily in addition to four monitored, 45-min sessions of stationary cycling weekly for 8 weeks found no improvements in LVESV, LVEDV, or LVEF as assessed by CMR [75]. Overall, the available data suggest that cardiac rehabilitation is safe, while its long-term effects on LV remodeling remain uncertain.

Emerging Considerations

The development and widespread adoption of early perfusion strategies, neurohormonal blockers, and device-based therapies have led to more contemporary evidence showing rather modest increases in ventricular volumes and reductions in EF [76]. Despite these modest changes in remodeling parameters, the incidence of HF, with its associated morbidity and hospitalization, remains high in this population [76]. This observation not only may be driven by a combination of direct ischemic-induced cardiomyopathy, but also may be due to increasing prevalence of HF with preserved EF. Further investigation needs to be undertaken to understand if there may be adjuncts to the traditional mechanistic model of infraction-related remodeling and whether other mechanisms after myocardial injury may promote a HF

with preserved EF phenotype. Such investigation is particularly important given the lack of current evidenced-based therapies for patients with HF with preserved EF. Furthermore, identification of patients at greatest risk of adverse cardiac remodeling and subsequent HF after MI may be important in prompting more aggressive initiation and uptitration of HF therapies. Infarct size measured as early as prior to index hospital discharge has been shown to correlate with adverse cardiac remodeling at 1 year [77]. Perhaps, early assessment with imaging modalities with more precise measures of infarct size, such as CMR, may be important in routine practice to assess patients at greatest risk for systolic dysfunction. In addition, if indeed there is a greater prevalence of HF with preserved EF in the post-MI population, more aggressive screening of this population for impaired lusitropy may be important, particularly if new therapies are found to be efficacious in this patient population.

Future Therapies

The use of the angiotensin receptor-neprilysin inhibitor (ARNI), sacubitril/valsartan, compared to conventional RAAS inhibitors, has been shown to further reduce all-cause and CV mortality and hospitalizations for HF in ambulatory HF patients with reduced EF [78]. The effects of ARNI therapy have already shown beneficial effects on LV remodeling post-MI in rats [79]. The PARADISE-MI study (NCT02924727), a large extension trial of sacubitril-valsartan in the post-MI setting, will plan to enroll over 4500 patients randomized to sacubitril/valsartan vs. ramipril with the primary outcomes being the composite of CV mortality, HF hospitalization, or worsening HF in the outpatient setting. PROVE-HF (NCT02887183) will plan to enroll 830 HF patients with reduced EF and assess the impact of sacubitril/valsartan on changes in NT-proBNP and LVESV index at 12 months [80••]. Studies will assess the impact of sacubitril/valsartan in chronic HF with preserved EF. Follow-up studies should assess the impact of sacubitril/valsartan specifically on remodeling parameters in the post-MI population.

Cell-based approaches may be an important emerging therapy in the treatment of post-infarction HF. Current studies have offered mixed results [81–83]. These therapies, combined with a new emphasis on material science and tissue engineering, may play an important role in the treatment of post-MI cardiomyopathy in the years to come. A more complete review of challenges and opportunities associated with these therapies has been previously published [84].

Conclusion

In summary, post-MI LV remodeling has been previously well studied and involves complex pathophysiological interactions between cellular components, signaling molecules, the ECM, and neurohormonal regulation. While adverse LV remodeling has been variably defined via the use of multiple imaging modalities, it has universally been associated with poor clinical outcomes. Multiple therapeutic targets exist to stop adverse remodeling and promote reverse remodeling, including early revascularization, optimal medical therapy with neurohormonal antagonists, and cardiac resynchronization therapy in appropriately selected patients. Further therapies are currently under investigations in the post-MI population and may provide incremental benefit to existing therapies.

Compliance with Ethical Standards

Conflict of Interest Eric J. Velazquez reports grants from NHLBI, personal fees from Abiomed, grants from Alnylam Pharmaceuticals and Bay Laboratories, grants and personal fees from Amgen, personal fees from Expert Exchange, personal fees from Merck & Co., grants and personal fees from Novartis Pharmaceutical Corp, and grants from Pfizer.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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