Left ventricular remodelling post-myocardial infarction: pathophysiology, imaging, and novel therapies

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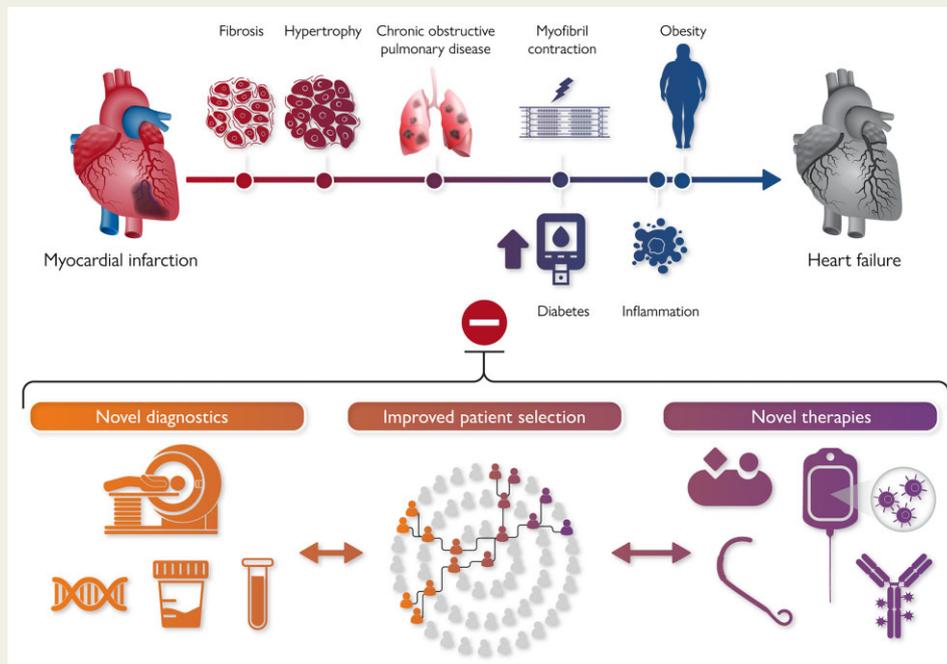
After a cardiac injury, comorbidites and various pathophysiologic mechanisms contribute to left ventricular remodelling and heart failure. Strategies to improve patient care beyond currently available treatment algorithms should include novel diagnostics, improved and treatment specific patient selection as well as novel therapies.

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Abstract

Most patients survive acute myocardial infarction (MI). Yet this encouraging development has certain drawbacks: heart failure (HF) prevalence is increasing and patients affected tend to have more comorbidities worsening economic strain on healthcare systems and impeding effective medical management. The heart's pathological changes in structure and/or function, termed myocardial remodelling, significantly impact on patient outcomes. Risk factors like diabetes, chronic obstructive pulmonary disease, female sex, and others distinctly shape disease progression on the 'road to HF'. Despite the availability of HF drugs that interact with general pathways involved in myocardial remodelling, targeted drugs remain absent, and patient risk stratification is poor. Hence, in this review, we highlight the pathophysiological basis, current diagnostic methods and available treatments for cardiac remodelling following MI. We further aim to provide a roadmap for developing improved risk stratification and novel medical and interventional therapies.

Keywords   Remodelling • Fibrosis • Heart failure • Myocardial Infarction

Introduction

Heart muscle comprises three important components that enable efficient contraction: cardiomyocytes, capillaries, and extracellular matrix (ECM), which consists of different collagen fibre types and provides structural integrity. Left ventricular (LV) remodelling describes the heart's (mal)adaptation to mechanical, neurohormonal, and inherited changes by regulating ventricular size, shape, and function. While cardiomyocyte growth orchestrated by increased microcirculatory blood supply (e.g. during pregnancy, growth, or athletic training) is considered physiological and completely reversible, 'adverse' or 'pathological' remodelling following myocardial infarction (MI) confers disproportionate risk for heart failure (HF) and significantly decreases survival.[1] This review focuses on pathophysiology, imaging, and management of LV remodelling preceding HF development. To date, therapies have sought to improve 'mechanics' (preload, afterload) and adjust molecular mechanisms of remodelling; novel treatment targets can encompass both strategies (*Figure 1A*).

Epidemiology

Over the last decade, HF prevalence increased.[2,3] Despite timely urgent revascularization and subsequent treatment strategies that significantly lower the mortality of acute MI, ischaemic heart disease remains the perennial cause of HF.[2,3] Comorbidities predict HF development and severity. Indeed, >50% of HF patients have more than seven comorbidities,[4,5] advanced age and female sex being the strongest individual HF predictors. Likewise, mortality post-MI correlates with advanced age, independent of infarct size,[6] possibly because of a higher prevalence of cardiac hypertrophy but the reduced immune response, scar formation, and autophagy in senile hearts.[7] Women are disproportionately affected by comorbid conditions.[8] Concomitant diabetes makes women three times more likely to develop HF compared with men.[9] Additionally, women are more likely to be obese and excess fat distribution is more disadvantageous following menopause, driving systemic inflammation.[10] Other comorbidities conferring a significantly higher risk of developing HF post-MI are hypertension, chronic kidney disease (CKD), and chronic obstructive pulmonary disease (COPD). Predictors of improved left ventricular ejection fraction (LVEF) are HF duration <1 year, higher pre-discharge blood pressure and higher baseline LVEF.[11]

Pathophysiology

Understanding key pathophysiological mechanisms is essential for two reasons. Firstly, these mechanisms could source novel therapeutic targets. Secondly, some mechanisms can be used for diagnostic and prognostic purposes (biomarkers, imaging) to better tailor and adjust future medical treatment.

Changes in left ventricular geometry

Geometrical changes are a major stimulus for LV remodelling and the '*Law of Laplace*' explains their progressive nature. Put simply, ventricular wall stress is directly related to LV pressure and radius and inversely proportional to twice the LV wall thickness. In the acute, early phase of MI, previously viable tissue decays, leading to loss of contractile function and secondarily increased LV volumes which in turn elevate wall stress and oxygen consumption. Weeks to months after MI, cardiac workload rises as the heart tries to compensate for higher pre- and afterloads.[12]

Myocardial hypertrophy

Myocardial hypertrophy is a distinct response to elevated workload and typically describes the volume expansion of terminally differentiated cardiomyocytes. This physiological, transient mechanism reduces wall stress and oxygen consumption to maintain cardiac output, as seen in pregnant and athletic individuals. Importantly, this process can occur and disappear without any permanent damage. On the contrary, pro-hypertrophic molecular pathways chronically triggered by either pressure/volume overload or MI frequently lead to overt HF. Physiologic hypertrophy proportionately expands chamber dimensions and wall thickness and since it includes adequate vascularization and no fibrosis, does not induce a specific pathological gene pattern.[13] Conversely, pressure overload typically produces significant fibrosis paired with disproportionate increases in wall thickness compared with ventricular volumes, leading to activation of foetal genes, and HF associated with systolic and diastolic dysfunction.[14]

Myocardial fibrosis

Myocardial fibrosis inarguably influences LV remodelling. Fibrosis can be separated into two main groups, with considerable overlap.[15] Interstitial fibrosis, which tends to occur earlier in response to various stimuli, describes collagen deposition by differentiated myofibroblasts and is, in principle, reversible. Replacement fibrosis, however,
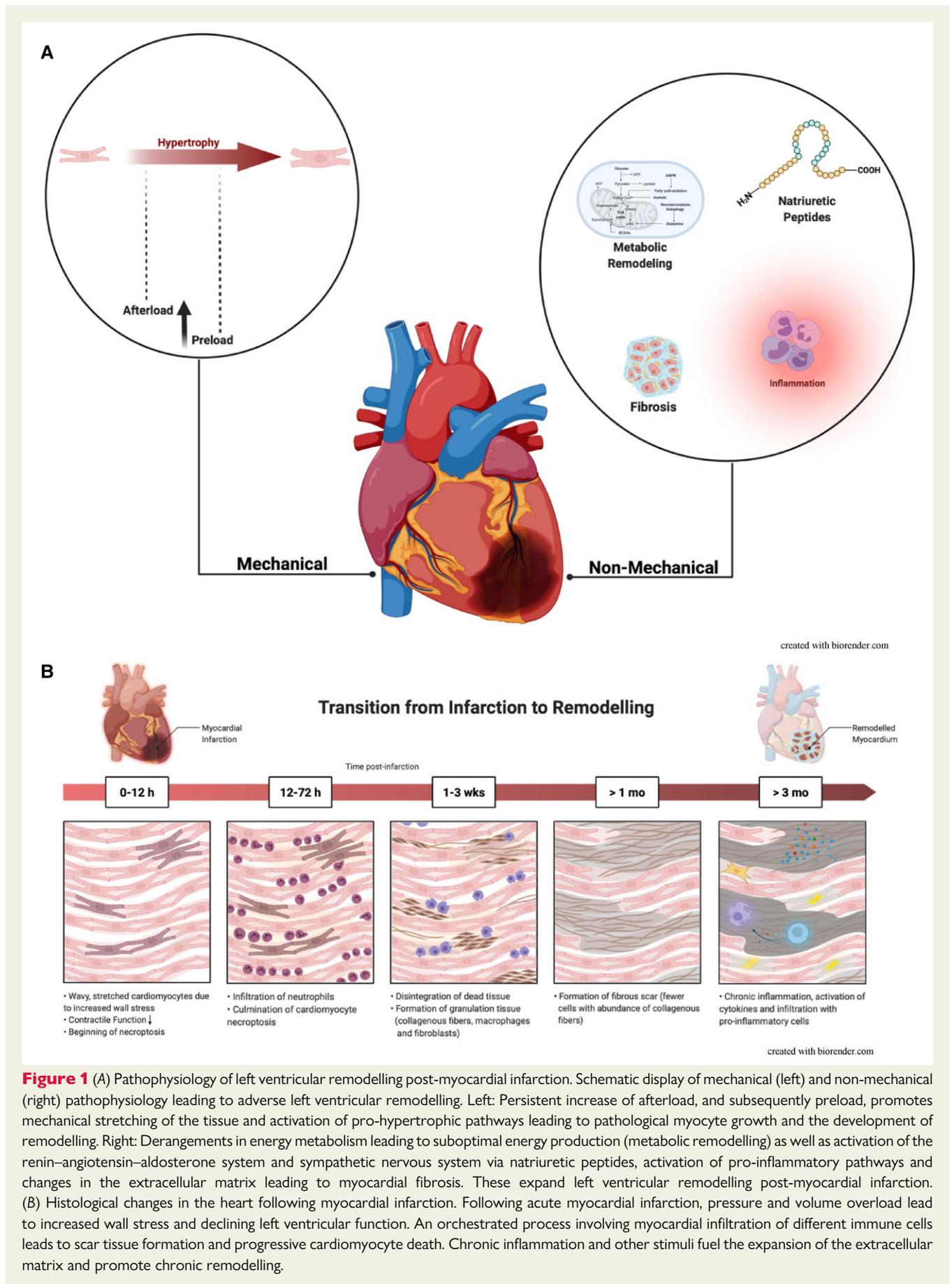
Figure 1 (*A*) Pathophysiology of left ventricular remodelling post-myocardial infarction. Schematic display of mechanical (left) and non-mechanical (right) pathophysiology leading to adverse left ventricular remodelling. Left: Persistent increase of afterload, and subsequently preload, promotes mechanical stretching of the tissue and activation of pro-hypertrophic pathways leading to pathological myocyte growth and the development of remodelling. Right: Derangements in energy metabolism leading to suboptimal energy production (metabolic remodelling) as well as activation of the renin–angiotensin–aldosterone system and sympathetic nervous system via natriuretic peptides, activation of pro-inflammatory pathways and changes in the extracellular matrix leading to myocardial fibrosis. These expand left ventricular remodelling post-myocardial infarction. (*B*) Histological changes in the heart following myocardial infarction. Following acute myocardial infarction, pressure and volume overload lead to increased wall stress and declining left ventricular function. An orchestrated process involving myocardial infiltration of different immune cells leads to scar tissue formation and progressive cardiomyocyte death. Chronic inflammation and other stimuli fuel the expansion of the extracellular matrix and promote chronic remodelling.

denotes collagen deposition following myocyte necroptosis and is considered irreversible. Following MI, the development and stimulation of collagen-producing myofibroblasts lead to progressive replacement fibrosis. Myocardial fibre stretching and the presence of inflammation are essential triggers for myofibroblast activation. Inflammatory reaction regulation is a finely tuned process as fibrosis is needed for sufficient scar formation but in excess will stiffen the heart, impairing oxygen diffusion, and thus hindering adequate oxygen supply. Fibrosis composition is tightly regulated by inflammatory and other cell types, paracrine mechanisms (e.g. transforming growth factors), and collagen-degrading enzymes like matrix metalloproteinases (MMPs). Detailed descriptions of molecular and cellular changes in the ECM exceed the scope of this review.[16]

Myocardial regeneration and proliferation

Cardiomyocyte necrosis precedes HF development. Research over the last two decades has, therefore, tried to compensate for myocyte loss by enhancing the regeneration of healthy myocardium. Zebrafish and, shortly after birth, also mammalian hearts can completely regenerate after cardiac injury,[17] a capacity that, under certain circumstances, can be prolonged up to 4 weeks after birth.[18] Yet the pathophysiologic principles underlying this complete regeneration remain largely elusive.[19]

Inflammation

A plethora of evidence confirms that MI triggers an inflammatory response which is primarily an orchestrated physiological process.[20] Necrosis and apoptosis are essential to this process and occur simultaneously but nevertheless confer distinct changes. Apoptosis, programmed cell death without intracellular constituent release, happens either intrinsically when the cell detects damage or extrinsically after inflammatory cell interacts with so-called 'death receptors'. Necrosis, the immediate predominant phenotype during MI, is an uncontrolled form of cell death with cell rupture. The released intracellular components activate the immune system via innate immune receptors. Inflammatory cells subsequently infiltrate to help clear the necroptotic cells and initiate a remedial response, thereby allowing adequate scar tissue formation.[21] This complex response involves a variety of inflammatory cell types at different timepoints (*Figure 1B*). Some cell subtypes are pro-inflammatory and others mediate healing, and their differentiation and interaction are tightly regulated. Myocardial injury induces cardiac infiltration by neutrophils and macrophages that eliminate cell debris, drive inflammation by producing pro-inflammatory cytokines and further attract pro-inflammatory cells. After several days, neutrophils vanish and remedying macrophages appear, while T-cells regulate monocyte activation, which is pivotal for cardiac healing.[22,23] T-cell activation takes place in heart-draining lymph nodes by autoantigens released from necroptotic myocytes, among other sources.[24] In the final 're-modelling phase', after the formation of solid scar tissue, the non-infarcted myocardium recruits progressively more inflammatory cells.[20] This chronic cytokine activation and myocardial infiltration by inflammatory cells can also be detected in HF patients. There are very limited experimental data on the underlying pathological changes and clinical implications of this chronic phase.[25] However,

the immune system might play a dual role: a chronic pro-inflammatory state drives maladaptive remodelling, whereas pro-angiogenic factors might contribute to healing.

Ischaemia/reperfusion injury and reactive oxygen species

Urgent coronary intervention in patients with ST-elevation MI (STEMI) is unequivocally beneficial, salvaging myocardium, reducing infarct size, and attenuating adverse LV remodelling. Paradoxically, inducing reperfusion to restore myocardial blood flow can expand infarct size, the so-called reperfusion injury, depending on ischaemia duration, severity, and residual blood flow level (for review see Heusch[26]). On a molecular level, succinate accumulation during ischaemia is suddenly oxidized following reperfusion, a process which ultimately mediates reactive oxygen species production.[27] Chronically elevated generation of oxygen radicals may induce a vicious cycle of cardiac hypertrophy, myocyte death, and further remodelling via MMP activation.[28] These changes lead to chronic mitochondrial remodelling, reduced energy production, and ultimately promote HF development.

Energy metabolism and mitochondria

Progressive metabolic remodelling is a pivotal driver of the transition to HF following MI.[29] While it remains to be determined whether post-MI (mal)adaptive metabolic changes are causally responsible, it is clear that metabolic alterations aggravate LV remodelling development and progression. During periods of reduced oxygen supply (i.e. ischaemia), the heart enhances its glycogen storage and increasingly relies on glycolysis for more oxygen-efficient energy production.[30] The peri-myocyte milieu (e.g. pressure overload, inflammation, hypoxia, etc.) and substrate availability regulate upstream genes resulting in a preference for carbohydrates over fatty acids for energy provision. This is a defining feature of the hypoxic antenatal cardiac energy metabolism.[31] Interestingly, repressing certain genes can revert the adult heart to this metabolic state, termed foetal gene pattern.[32] Unfortunately, insulin resistance significantly reduces the availability of intracellular glucose, thereby activating mTOR and further promoting the development of fibrosis and apoptosis.[33,34] Elevating fat oxidation and reducing over-reliance on glucose prevents remodelling and increases myocardial efficiency, possibly by restoring metabolic flexibility/homeostasis.[35,36] In addition to substrate-level changes, acutely accumulated lactate leads to cytosolic and subsequently mitochondrial calcium overload which facilitates mitochondrial membrane leakage, decreasing both energy production and expression of pro-necroptotic and pro-inflammatory molecules (e.g. cytochrome c).[37]

Neurohormonal activation

The sympathetic nervous system (SNS) and renin–angiotensin–aldosterone system (RAAS) evolved to maintain cardiovascular equilibrium. When continuously activated by elevated circulating angiotensin II, the SNS and RAAS promote HF development, adverse remodelling and cell death in murine models.[38,39] Moreover, SNS and RAAS activation levels in patients correlate with severity and outcomes in HF and predict poor prognosis.[40–42] Impeding the

deleterious effects of SNS and RAAS activation are the mainstay of present-day pharmacological HF treatment.[43]

Cardio-renal interplay

The close interplay between the heart and kidneys, often referred to as the cardio-renal axis, is key to HF development and progression.[44] Multiple pathomechanisms, like oxidative stress and inflammation that are individually relevant for CKD and HF may also contribute to cardio-renal interplay; this is reviewed in more detail elsewhere.[45] Mounting evidence, including from experiments using radiofrequency renal denervation (RDN), suggests direct cardio-renal interactions.

Natriuretic peptides

Increasing wall stress and stretching peri-MI leads to natriuretic peptide (NP) secretion from atrial and ventricular cardiomyocytes. The three identified isoforms, A-type NP (ANP), B-type NP (BNP), and C-type NP (CNP),[46,47] primarily act as endocrine hormones and modulate diuresis, natriuresis, vasodilation, and inhibition of the SNS and RAAS.[48,49] Additionally, certain NPs, such as BNP and NT-proBNP, are excellent prognosis predictors in patients after MI.[50] Natriuretic peptide concentrations can reflect pro-fibrotic environments and could be used to stratify individuals at risk for remodelling, a patient group that currently cannot be adequately assessed by conventional imaging methods.[51,52] Beyond their endocrine effects, NPs can also counter the negative impact of angiotensin II and endothelin-1 pro-hypertrophic signalling and seem to have an autocrine regulatory effect on myocyte size.[53] A-type NP inhibits collagen synthesis, the main driver of cardiac fibrosis.[54] Interestingly, pre-emptively injecting recombinant human BNP prior to coronary stent implantation appears to confer some degree of protection from myocardial injury, highlighting the NPs' therapeutic potential.[55]

Imaging

In recent years, non-invasive cardiac imaging has significantly advanced, providing a range of increasingly accurate and sophisticated tools to characterize ventricular remodelling *in vivo*. As methodology has evolved, clinical applications have expanded. The primary purpose of clinical imaging remains to identify the presence and severity of remodelling in a given patient by assessing ventricular function and geometry using echocardiography or cardiac magnetic resonance (CMR). In clinical routine, echocardiographic biplane summation-of-disks methods are the standard two-dimensional (2D) volume measurement technique. If available and applied by experienced operators, the use of three-dimensional (3D) LV volume and function assessment is preferred over the summation-of disk method due to the better reproducibility.[56] However, 3D techniques are heavily reliant on excellent imaging quality.[57] Endocardial delineation can be further improved by the application of contrast media which enables levels of reliability when measuring ventricular function comparable to those of CMR.[58] While CMR remains the gold standard for LV volume measurements, it is not as widely available, not easily applicable in patients with cardiac implanted devices and needs longer examination time when compared with routine echocardiography. Serially examining cardiac function and geometry

may also help monitor the success of any given treatment strategy. Especially in Phase II clinical trials, more advanced and reproducible repetitive measurements of LV geometry (contrast echo, 3D echo, CMR) can help to improve detection of small treatment differences, understanding of mechanisms of action, and thereby improve patient selection for costly randomized Phase III trials.[59] Yet, modern imaging has more to offer. Further steps after gross identification of remodelling may include (i) assessing cardiac and non-cardiac comorbidities as potential treatment targets, (ii) analysing aetiologic mechanisms of remodelling, (iii) evaluating the individual risk of disease progression and adverse outcomes, and (iv) specifically detecting targets for tailored therapies.[60] To achieve these goals, an ever-increasing spectrum of advanced techniques such as strain imaging, CMR tissue characterization, and radionuclide-based molecular imaging is emerging, thereby establishing a foundation for implementing advanced personalized treatment strategies.[61] *Table 1* provides an overview of concurrent imaging applications in ventricular remodelling. Specific features of and recent developments in available methodologies are summarized below.

Echocardiography

Standard 2D echocardiography is the first-line method to detect remodelling by determining contractile dysfunction and bi-ventricular geometry in clinical routine. Historically, HF is classified primarily by LVEF quantification,[43] but additional functional parameters help define the severity of remodelling and may guide device therapies such as implantable cardioverter defibrillators (ICD) and cardiac resynchronization (CRT). Strain imaging allows more detailed analysis of myocardial contractility and provides excellent prognostic value in HF (*Figure 2A*). Trans-oesophageal and 3D echocardiography help detecting acquired valvular heart diseases such as ischaemic valvular regurgitation. Certainly, secondary/functional mitral regurgitation is associated with adverse HF outcomes and thus, may be a potential therapeutic target.[62] Right ventricular (RV) assessments to further characterize remodelling and prognosis include functional parameters like tricuspid annular plane systolic excursion and fractional area change as well as Doppler methods. Effects can be two-fold as HF is regularly accompanied by pulmonary hypertension and pulmonary hypertension can equally worsen HF. This may further influence individualized therapeutic strategy.

Cardiovascular magnetic resonance

With the development of faster non-breathold sequences and highly reproducible post-processing, CMR remains the gold standard for assessing cardiac anatomy and function, particularly in patients with difficult anatomy (e.g. obesity, inherited disorders, etc.).[63] Cardiac magnetic resonance not only detects the presence and severity of remodelling but also offers an array of novel approaches for differentiation of infarcted, viably injured, and non-infarcted myocardium (*Figure 2B*). Sophisticated techniques such as strain encoded-imaging or post-processed feature tracking can quantify myocardial deformation to gain information comparable to that provided by echocardiographic strain imaging.[64,65] Cardiac magnetic resonance-measured LV volumes and certain infarct characteristics provide incremental post-MI prognostic information beyond LVEF.[66] Cardiac magnetic resonance's unique feature is its capacity to characterize myocardial tissue composition in order to determine reversible vs. irreversible

Table 1 Non-invasive imaging modalities for assessment of left ventricular remodelling

Imaging modality	Benefits	Limitations	Treatment/development implications
Echocardiography			
2D	• Widely available • Low-cost • Fast acquisition • Well tolerated by patients • Bedside studies possible	• Significant inter-individual and inter-operator variability • Challenging in patients with comorbidities (e.g. obesity)	• Guides medical therapy • Guides device therapy • Method of choice for clinical routine
3D	• Increased accuracy • Representative even in altered ventricular geometry	• High level of operator experience required • Additional post-processing necessary • Not widely available	• Guides special interventions for acquired (ischaemic) valve disease
Contrast echo	• Improved accuracy and reproducibility	• Requires 'expert knowledge' and frequent exposure to the method • Likely limited to experienced centres • Time consuming	• May improve earlier detection of LV remodelling and thus, facilitate earlier treatment
CMR			
Imaging	• Gold standard for assessment of cardiac volumes and function • High reproducibility, low variability • Multi-organ imaging • Possibly reduction in sample size for clinical trials • RV and valve assessment independent of anatomy	• Resource and cost intense • Limited availability • Longer acquisition • Reduced patient compliance (e.g. claustrophobia) • Prone to artefacts due to implants (devices, valves, etc.)	• Provides excellent assessment quality for challenging cases • May identify reversible causes of remodelling
LGE	• Non-invasive assessment validated histologically • Assessment of viability/MVO, ischaemia, blood flow and fibrosis • Equally potent for clinical and research applications	• Prone to breathing artefacts • Limited suitability for patients with severe renal disease • Possible long-term deposition of gadolinium in cerebral tissue	• Territory guided revascularization • Anti-fibrotic therapies
Parametric mapping	• Native T1-mapping can determine the aetiology of cardiac injury • Contrast-enhanced T1-mapping enables the calculation of ECV for diffuse fibrosis • T2*-mapping can detect IMH/MVO	• Parametric mapping sequences are largely research techniques without clinical validation • Prone to artefacts by breathing or arrhythmia • Sequences and values not universally agreed across different vendors/systems	• May allow identification and phenotypization of subgroups benefitting from intensive and early treatment • Assessment of area at risk and scar size post-infarction may improve risk stratification
MR spectroscopy	• Investigation of high-energy phosphate metabolism and mitochondrial function (^{31}P-MRS) • *In vivo* assessment of metabolic pathways (hyperpolarized MR)	• Only applied in the research setting • Requires centre-experience and specialist input and equipment	• Early identification of treatment response • Possibly reducing cost for drug development by providing early *in vivo* readouts with limited patient numbers
Nuclear imaging			
SPECT/PET	• Plethora of molecular radiolabelled molecules allows *in vivo* assessment of perfusion, metabolic substrate usage and inflammation • Multi-organ assessment • Improved assessment of treatment response	• Currently research use mostly • Costly and resource intense • Limited availability of tracers	• Image-guided molecular therapy • Identification of novel targets and biomolecules

2D, two dimensional; 3D, three dimensional; ^{31}P-MR, ^{31}phosphorus magnetic resonance; CMR, cardiac magnetic resonance; Echo, echocardiography; ECV, extracellular volume, IMH, intramyocardial haemorrhage; LGE, late gadolinium enhancement; MRS, magnetic resonance spectroscopy; MR, magnetic resonance; MVO, microvascular obstruction; PET, positron emission tomography; RV, right ventricle; SPECT, single photon emission computed tomography.
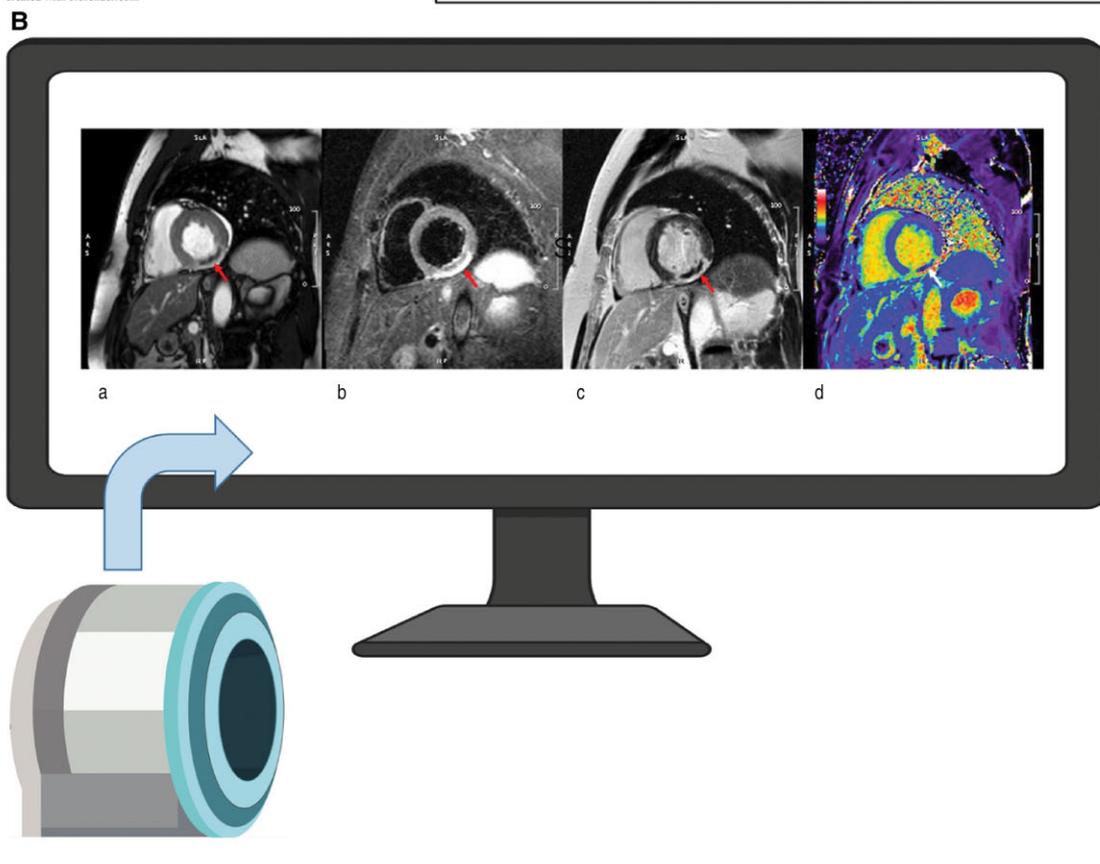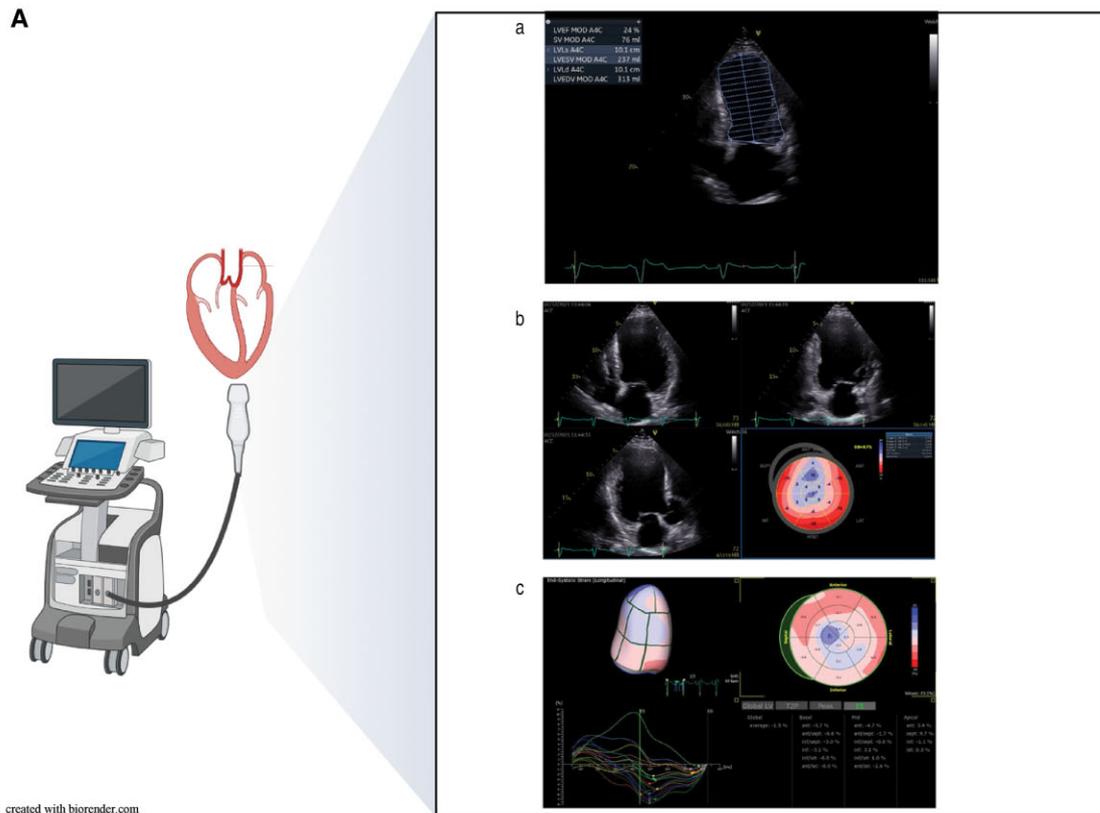
Figure 2 (*A*) Detection and severity assessment of left ventricular remodelling by transthoracic echocardiography. (*a*) Quantification of left ventricular function showing severely reduced left ventricular ejection fraction, enlarged volume, and an apical aneurysm. (*b*) Assessment of myocardial

injury: T2-imaging can show inflammation indicating reversible injury, while diffuse fibrosis identified by e.g. T1-mapping and/or focal scar revealed by late gadolinium enhancement (LGE) imaging demonstrate irreversible damage. Scar detection by LGE enables differentiation between ischaemic and non-ischaemic aetiology of HF. Furthermore, LGE is the reference standard for assessing myocardial viability and is used to guide coronary revascularization. Additionally, LGE can provide useful information for patient selection for CRT, as myocardial scar presence may be correlated to lower CRT response in patients with ischaemic heart failure with reduced ejection fraction (HFrEF).[43] Equally, LGE facilitates early identification of papillary muscle infarction which may predict functional mitral regurgitation and adverse outcome post-STEMI. [67,68]

Effective treatment of MI patients with non-obstructive coronary arteries (MINOCA) remains a major challenge. Even though MINOCA occurs in up to 13% of all MIs, its mechanisms are poorly understood and little is known about either the development of remodelling or prognosis in MINOCA patients.[69] Cardiac magnetic resonance is an ideal technique for investigating the underlying aetiology and monitoring therapy to avoid progressive adverse remodelling e.g. by an undiagnosed scar.[70,71]

Importantly, LGE can also be used to identify post-MI microvascular obstruction (MVO) and/or intramyocardial haemorrhage (IMH) by visualizing the no-reflow phenomenon, which reveals an area of the infarct region with hypoenhancement indicating no blood supply despite successful revascularization. As this indicates a region of particularly severe damage, multiple underlying mechanisms such as increased inflammation-induced tissue pressure, arteriole occlusion, and haemorrhage due to capillary leakage may contribute to infarct expansion and thereby progression of adverse remodelling.[72]

Beyond LGE, MVO, and IMH, CMR tissue mapping may provide even more depth for phenotyping MI patients at risk for remodelling. The area at risk, characterized by the relation between T2-mapping-derived oedema and LGE-defined scar size after MI, predicts the outcome. Assessing alterations in non-infarcted myocardium by quantitative parametric mapping using a combination of T1-mapping and LGE also adds novel information on outcomes.[73]

Native T1-mapping may indicate different aetiologies of cardiac injury, whereas the calculation of extracellular volume (ECV) based on contrast-enhanced T1-mapping is often considered to be more specific for diffuse fibrosis.[74] T2*-mapping is a novel technique for characterizing tissue iron content to identify a distinct subgroup of STEMI patients with IMH, which compromises myocardial salvage and drives infarct expansion after reperfusion.[75] An approach combining MVO

and IMH assessment with strain imaging was able to predict long-term recovery in STEMI patients after early beta-blocker therapy.[76]

Very recently, oxygenation-sensitive CMR identified inflammatory reactions, an important pathophysiologic mechanism driving adverse remodelling, in STEMI patients.[77]

Radionuclide-based molecular imaging

Nuclear cardiology employs radiolabelled biomolecules for non-invasive *in vivo* visualization. Unlike echocardiography or CMR, this method is not routinely used to detect remodelling or assess its severity. While standard clinical imaging of tissue perfusion and viability may help evaluate aetiology and guide revascularization, the development and implementation of novel molecular-targeted strategies have significantly advanced radionuclide imaging methodologies.[78] The spectrum of molecular-targeted radiopharmaceuticals has been continuously growing, expanding the number of biological pathways that can be non-invasively interrogated by conventional scintigraphy or positron emission tomography (PET). Using the glucose analogue ^{18}F-deoxyglucose, fatty acid analogues such as ^{11}C-palmitate or the trycarboxylic acid cycle substrate ^{11}C-acetate, PET elucidates detailed insights into metabolic substrate utilization and myocardial efficiency, and enables sensitive quantification of various drugs' modifying effects.[79–81] Furthermore, radiolabelled catecholamines can identify impaired myocardial sympathetic innervation, both in general and specifically in the viable infarct border zone, where it is a marker of arrhythmogenic risk and HF progression.[82–84] As myocardial inflammation and fibrosis play key roles in repairing injured myocardium, their molecular hallmarks have emerged as targets for novel tracer-based approaches. These include targeted imaging of the chemokine receptors CXCR4[85] and CCR2,[86] somatostatin receptors,[87] the mitochondrial 18kD translocator protein TSPO,[88] or other pro-inflammatory targets.[89] Fibroblasts and the ECM may be interrogated through ligands binding to integrins, MMP[90] or fibroblast activation protein.[91] The tracer principle of nuclear cardiology theoretically facilitates labelling and visualizing almost any therapeutic molecule,[92] nanoparticle or cellular system[93] for non-invasive tracking of *in vivo* biodistribution and target area accumulation. Such molecular imaging approaches have so far been primarily applied to mechanistic studies, drug development, or trials of therapeutic effectiveness. However, as novel molecular therapeutics (RNA products, cells, nanoparticles) are costly and may not be beneficial in every disease stage and every individual, personalized and more complex diagnostic testing algorithms may be required (*Figure 3*). More specific molecular imaging-guided drug therapies

Figure 2 Continued

deformation using two-dimensional strain imaging (same patient). The bulls-eye plot of segmental longitudinal strain is a composition of individual two-dimensional acquisitions and displays dyskinetic segments in blue. (*c*) Three-dimensional strain imaging provides simultaneous assessment of strain throughout the cardiac cycle in all myocardial regions, summarized in a volumetric display and a bulls-eye plot, with dyskinesia displayed in blue. (*B*) Post-infarct myocardial tissue characterization by cardiac magnetic resonance imaging. Short-axis views of inferior subacute myocardial infarction acquired using a 1.5 T system. (*a*) Mid-systolic frame of a cine sequence after administration of contrast agent; dark area indicates microvascular obstruction (see red arrow). (*b*) T2-weighted image sequence where bright area represents peri-infarction oedema (red arrow); grey area sub-endocardially indicates the presence of microvascular obstruction. (*c*) Late gadolinium enhancement acquisition following administration of gadolinium-based contrast agent; bright areas (red arrow) represent tissue necrosis/scar formation with an encapsulated dark area indicating microvascular obstruction. (*d*) Modified Look–Locker inversion recovery T1-map following administration of contrast media with bright green/red areas corresponding to scar and dark blue areas indicating microvascular obstruction.
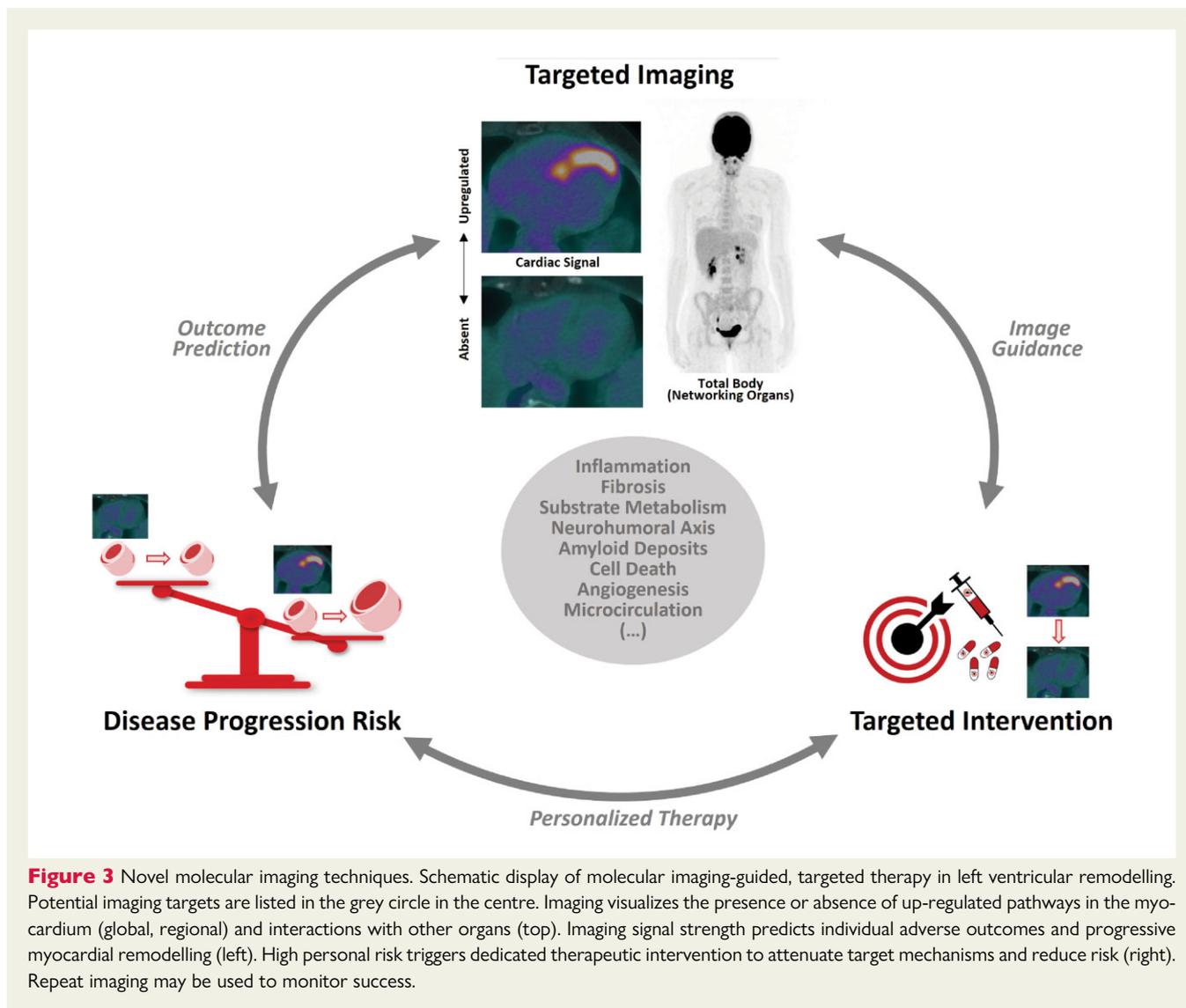
Figure 3 Novel molecular imaging techniques. Schematic display of molecular imaging-guided, targeted therapy in left ventricular remodelling. Potential imaging targets are listed in the grey circle in the centre. Imaging visualizes the presence or absence of up-regulated pathways in the myocardium (global, regional) and interactions with other organs (top). Imaging signal strength predicts individual adverse outcomes and progressive myocardial remodelling (left). High personal risk triggers dedicated therapeutic intervention to attenuate target mechanisms and reduce risk (right). Repeat imaging may be used to monitor success.

may prevent post-infarct LV remodelling based on individual disease biology. Recently, PET imaging using a CXCR4-ligand, ^{68}Ga-pentixafor, identified post-infarct inflammation as a marker of adverse outcome.[94–96] This information was subsequently used to administer the CXCR4-blocker plerixafor to improve function only when PET indicated high expression of the CXCR4 target in myocardial tissue.[94] This concept may be translated to other innovative pairs of imaging tests and drug interventions targeting distinct molecular or cellular mechanisms of cardiac repair and remodelling.[97]
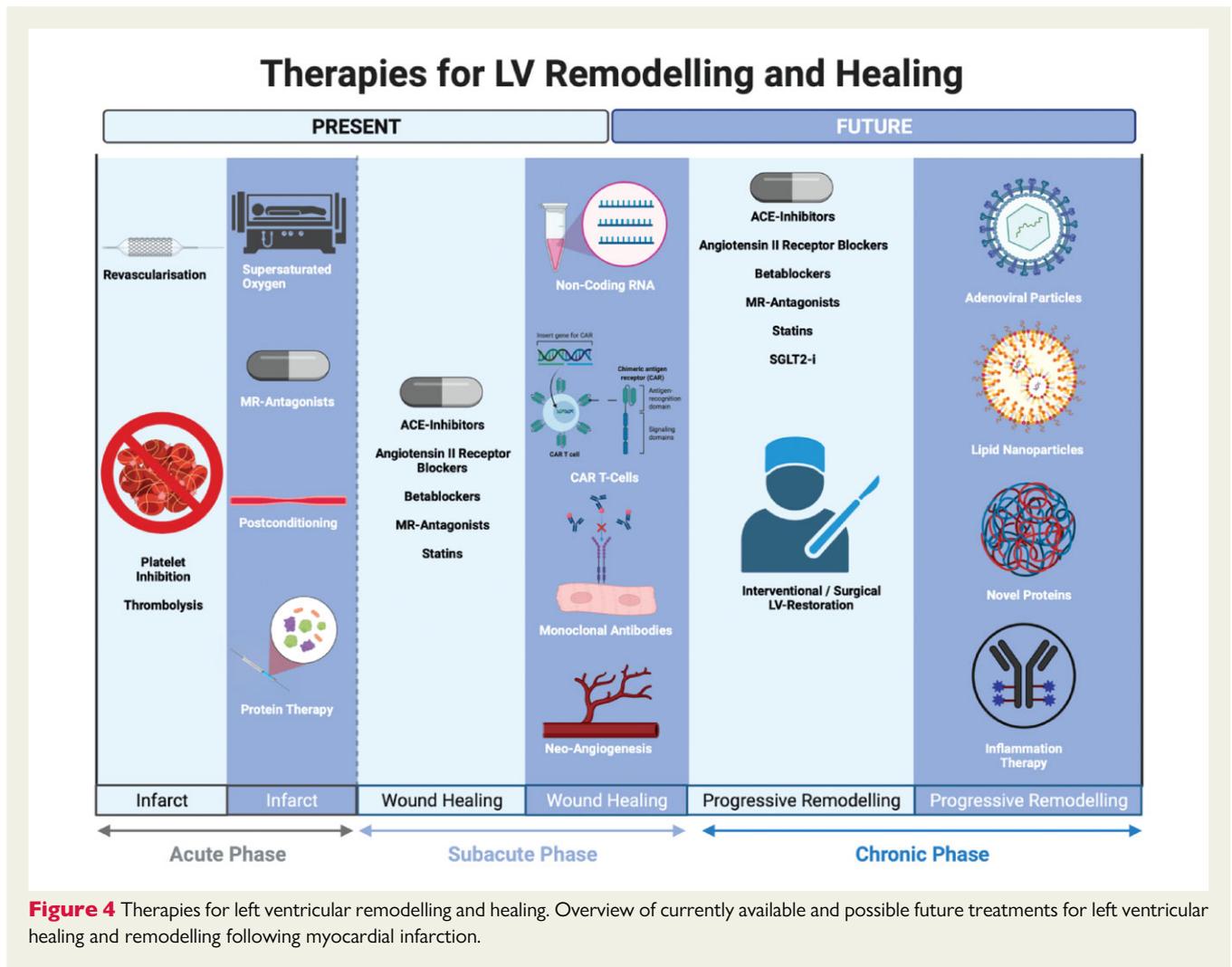
Lastly, another strength of molecular imaging is that because it relies on the systemic biodistribution of labelled molecules, radionuclide imaging readily provides information on the entire body. This enables systemic analysis of the interrelationships between the heart and other organs, which may both expand mechanistic insights and help determine individual risk. Examples include interactions between myocardial inflammation, the haematopoietic system, and atherosclerosis[98]; interconnections among myocardial inflammation, remodelling, and neuroinflammation[88,99]; or the role of inflammation in cardio-renal crosstalk.[100]

Management

The first-line strategy for avoiding maladaptive LV remodelling is to treat reversible causes: revascularization should be performed during both acute and chronic conditions, valvular heart disease corrected, and hypertension adequately treated. As outlined above, changes in filling state, preload, and afterload are important contributors to LV remodelling. Several HF medications, including RAAS blockade, address this mechanism. Further, multiple mediators of LV remodelling contribute to current and future treatment strategies, independently of their haemodynamic effects, as discussed below (*Figure 4*).

Neurohormonal inhibition

Neurohormonal inhibition for LV recovery, remodelling and HF after MI is a classic example of successful bi-directional 'bench-to-bedside' translational science. Rodent models of post-MI ventricular remodelling provided the impetus for investigating captopril in patients, ultimately leading to angiotensin-converting enzyme (ACE) inhibitors becoming the standard indication after MI.[101,102] Subsequently, in

Figure 4 Therapies for left ventricular remodelling and healing. Overview of currently available and possible future treatments for left ventricular healing and remodelling following myocardial infarction.
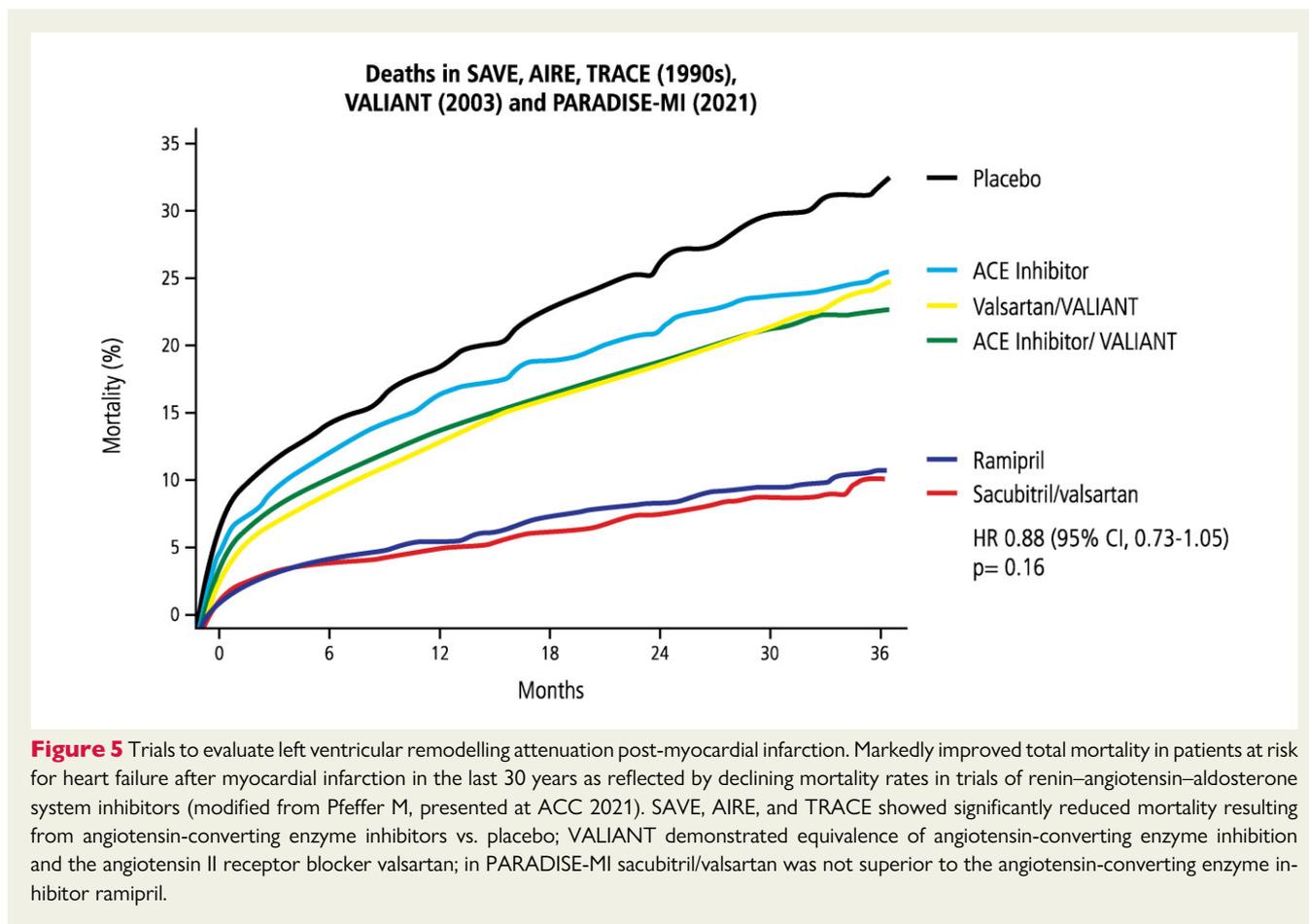
the VALIANT trial, valsartan commenced 0.5–10 days after acute MI in patients with HFrEF was as effective as captopril regarding total mortality, whereas combining both drugs increased the adverse event rate without improving survival.[103] The mineralocorticoid receptor agonist eplerenone improved LV remodelling in rats with LV dysfunction after large MI. Combination therapy with an ACE inhibitor substantially increased this effect by preventing LV fibrosis, cardiac hypertrophy, and molecular alterations.[104] These results provided mechanistic explanations for the reduced morbidity and mortality among patients with acute MI by eplerenone observed in EPHESUS.[105]

In addition to their anti-arrhythmic effects, betablockers also significantly improve LV remodelling, thereby lowering mortality and morbidity in patients with chronic HFrEF. However, despite recommendations to administer betablockers early to patients with acute MI, there is considerable controversy regarding if and how betablockers enhance LV healing and promote reverse remodelling post-MI. Recent work demonstrated that metoprolol, but not atenolol or propranolol, changed neutrophil dynamics and thus reduced infarct size and myocardial inflammatory infiltration in a mouse model of ischaemia/reperfusion.[106]

Angiotensin receptor-neprilysin inhibitors

Because RAAS blockade markedly improved cardiac remodelling post-MI and angiotensin receptor-neprilysin inhibitor treatment reduced mortality/morbidity more effectively than ACE inhibition in chronic HFrEF in PARADIGM-HF[107], subsequent trials sought to investigate the potential of sacubitril/valsartan in patients with HFrEF post-MI.[108,109] In PROVE-HF, sacubitril/valsartan in HFrEF patients led to notably better echocardiographic indices of cardiac volume and function, results that correlated with lower NT-proBNP levels.[110] In patients with asymptomatic LV dysfunction (EF ≤ 40%) ≥3 months after MI treated with ACE inhibition and betablockade, sacubitril/valsartan, compared with valsartan, did not significantly reduce the primary endpoint of LV end-systolic volume index (LVESVi) measured by CMR after 52 weeks.[108] The PARADISE-MI[109] trial randomized patients who survived acute MI and were at risk of developing symptomatic HF within 0.5–7 days to sacubitril/valsartan or ramipril. Compared to previous trials investigating ACE inhibitors or ARB post-MI, the event rates were substantially lower in PARADISE-MI, reflecting the totality of improved clinical care for these vulnerable patients (*Figure 5*). Sacubitril/valsartan did not

Figure 5 Trials to evaluate left ventricular remodelling attenuation post-myocardial infarction. Markedly improved total mortality in patients at risk for heart failure after myocardial infarction in the last 30 years as reflected by declining mortality rates in trials of renin–angiotensin–aldosterone system inhibitors (modified from Pfeffer M, presented at ACC 2021). SAVE, AIRE, and TRACE showed significantly reduced mortality resulting from angiotensin-converting enzyme inhibitors vs. placebo; VALIANT demonstrated equivalence of angiotensin-converting enzyme inhibition and the angiotensin II receptor blocker valsartan; in PARADISE-MI sacubitril/valsartan was not superior to the angiotensin-converting enzyme inhibitor ramipril.

significantly decrease the primary endpoints of adjudicated CV death or first worsening HF event but did limit both the total (including recurrent) adjudicated events as well as investigator-reported primary events.[111,112]

Sodium–glucose cotransporter 2 inhibitors/metabolism

Following the overwhelming success of sodium–glucose cotransporter 2 inhibitors (SGLT2-i) in patients with HF independent of underlying diabetes[113–115], several studies have investigated these drugs' potential to improve LV remodelling. In patients with HFrEF and Type 2 diabetes or prediabetes (SUGAR-DM-HF), empagliflozin vs. placebo was associated with reverse remodelling (reduced LVESVi and LVEDVi measured by CMR) and reduced NT-proBNP levels.[116] In non-diabetic pigs with MI induced by transient balloon occlusion of the LAD, empagliflozin ameliorated adverse remodelling, measured by CMR at 2 months.[117] Empagliflozin also switched post-MI myocardial fuel utilization away from glucose towards ketone bodies, free fatty acids, and branched-chain amino acids, thereby improving myocardial energetics. Two large trials are currently assessing SGLT2 inhibition in patients at risk for HF post-MI: EMPACT-MI (NCT04509674) includes 5000 patients with newly developed LVEF < 45% or signs/symptoms of congestion and, within 14 days after MI, randomizes them to receive 10 mg empagliflozin or placebo. The primary efficacy endpoint is the composite of time to first

HF hospitalization or all-cause mortality. DAPA-MI (NCT04564742) includes 6400 patients with reduced LVEF (<50%, randomized within 10 days after MI) and investigates whether 10 mg dapagliflozin vs. placebo reduces the primary composite endpoint of time to first HF hospitalization or CV death.

Treatment with the anti-ischaemic agent trimetazidine may normalize energy supply[118], reduce mitochondrial damage, and limit ischaemia/reperfusion injury in the acute MI phase.[119] Whether or not this treatment confers protection against chronic post-MI remodelling is currently under investigation.[120]

Statins

Interestingly, statins, a standard treatment post-MI, also improve LV remodelling. In rats with large MI, statin treatment attenuated LV dilatation and LV end-diastolic pressure and was associated with reduced myocardial expression of foetal genes and collagens.[121] These effects may be related to enhanced NO formation in statin-treated animals, as NOS inhibition abolished the positive results.[122]

Non-coding RNAs

Non-coding RNAs are important regulators of cardiac remodelling in chronic HF, post-MI and during pressure overload. Consequentially, silencing microRNAs *in vivo* using specific antisense inhibitors improves adverse myocardial remodelling.[123,124] In large porcine studies using CMR and detailed molecular analyses, treatment with

CDR132L, an antisense oligonucleotide drug directed against *miR-132* (applied on days 3 and 28 post-MI) effectively prevented maladaptive growth, inhibited remodelling and restored LV function.[125] Interestingly, delayed treatment after HF development (1 month post-MI) also significantly improved cardiac systolic and diastolic function and reversed cardiac remodelling at 3–5 months.[126] In a small clinical trial, *CDR132L* was well tolerated in patients with stable HF on standard medications and seemed to improve cardiac function.[127] *CDR132L* is now under investigation in a Phase II randomized, double-blind study in patients with reduced LVEF (≤45%) after MI.

Inflammation modulators

Although inflammation's pathophysiologic contributions to LV remodelling have been appreciated since the early 1990s, anti-inflammatory drugs are not yet standard of care for HF patients. Early on, anti-tumour necrosis factor (TNF) treatment was studied in a HF population;[128] however, all anti-TNF trials were futile, possibly due to poor patient selection and likely due to focusing on the wrong target, indicating the need for deeper pathophysiological understanding clinical trials. In recent years, a plethora of research has shown inflammation is pivotal during the remodelling process. Canakinumab, a monoclonal antibody targeting interleukin-1 beta, lowered CV events in a post-MI patient cohort,[129] the first trial in cardiovascular medicine that improved outcomes only by inhibiting inflammation. Canakinumab also lowered the HF hospitalization rate.[130]

Novel pathways could be addressed via T-cell modulation, for example by using specific antibodies or by chimeric antigen receptor (CAR) T-cell technologies recently described in animals.[131] Nanoparticles can facilitate targeted delivery of drugs and can be specifically designed to target inflammatory cells. In the cardiovascular field, though, nanoparticles have not yet been studied in patients.[132,133] Selecting individual patients in need of anti-inflammatory treatment, possibly identified by enhanced molecular imaging strategies, is likely key to successful therapy.

Protein therapies

While angiogenic growth factors have huge therapeutic potential after MI, all clinical trials have unfortunately yielded neutral results, and paracrine-acting proteins may not be suitable for treating (sub) acute MI (for review see Wu *et al.*[134]). A more promising approach may be continuously delivering growth factor by subcutaneous infusion. Indeed, in a murine model of reperfused acute MI, prolonged infusions of myeloid-derived growth factor (MYDGF C19orf10) or endoplasmic reticulum membrane protein complex subunit 10 (EMC10) have beneficially affected cardiac remodelling and function as well as survival,[135,136] though currently no clinical studies have been completed.

Gene editing and adenoviral and lipid nanoparticles

Over the past two decades, many attempts to improve outcomes post-MI have involved adenoviral-based gene therapy to induce angiogenesis in the ischaemic heart.[137] However, beneficial effects in clinical studies appeared to be limited to enhanced perfusion reserve and angina relief in patients with chronic myocardial ischaemia.[138,139] Genome-editing technologies have greatly progressed[140] and may enable regenerative therapies that prevent/treat adverse cardiac remodelling after MI. While initially limited by the need to use adenoviral vectors to achieve *in vivo* genome editing, lipid nanoparticle (LNP)-based transfer of ribonucleic acid (RNA) may be much better suited to clinical applications. Nevertheless, any gene-editing approach crucially depends on identifying a single gene that determines pathophysiology, which seems unlikely for the complex process of post-infarction cardiac remodelling. However, the recently described attenuation of myocardial fibrosis and hypertrophy in a mouse model of cardiac hypertrophy by LNP-based RNA transfer to generate transient anti-fibrotic CAR T-cells *in vivo*[131] may pave the way for addressing adverse remodelling post-MI.

Bone marrow-derived cell therapy

After encouraging early results from animal studies, bone marrow-derived cell (BMC) therapy was thoroughly investigated over the last 20 years and promoted as an innovative treatment for patients with STEMI. Regrettably, it now seems clear that this approach is not effective for acute MI, although there is still hope for potential application in refractory angina or chronic HFrEF.[141,142] Following the neutral results of the BOOST-2 trial,[143] neither the ALLSTAR nor BAMI trials detected significant benefits for BMC therapy in patients with MI.[144,145]

Transcatheter and surgical interventions

Addressing reperfusion injury hypothetically provides an attractive target to reduce infarct size and prevent adverse remodelling. Unfortunately, all strategies, such as ischaemic postconditioning, showing benefits in preclinical studies were futile in larger randomized controlled studies.[26] In smaller studies, intracoronary infusion of hyperoxaemic blood (supersaturated oxygen therapy) after PCI in patients with anterior STEMI was associated with reduced infarct size and may be related to improved outcomes,[146] but this method has not been subjected to large randomized studies to determine whether it can prevent or attenuate LV remodelling post-MI. Another potential way to reverse LV dilatation is surgical or interventional ventricular restoration. Surgically correcting LV geometry may be considered for large akinetic or aneurysmatic areas that increase wall stress. Despite the theoretical benefits of reconstructing normal LV architecture during surgical revascularization, this approach was not superior to revascularization alone.[147] Therefore, this treatment is reserved for narrowly selected HF patients who are either refractory to standard of care or present with severe, malignant arrhythmias. In patients with chronic anteroseptal infarctions, a transjugular and left thoracotomy technique introduces anchor pairs to plicate the anterior and free wall LV scar against the RV septal scar in order to decrease cardiac volume (Revivent™).[148] While results in carefully selected patients seem to be encouraging, randomized studies' findings are still pending (REVIVE-HF, NCT03845127). Another interventionally placed device (AccuCinch® system) is attached to the inner LV wall and then cinched to reduce LV dilatation. The randomized CORCINCH-HF study (NCT04331769) investigating the device is ongoing. In HFrEF patients, RDN data consistently suggest beneficial effects on symptoms, HF biomarkers, and exercise capacity in different

species.[149–151] Renal denervation also improves cardiac stiffness and vascular resistance in HFpEF.[152] Whether RDN augments post-MI remodelling and protects from HF development remains to be evaluated in clinical trials (COMBI-RDN, NCT02272920).

Conclusions

Left ventricular remodelling is an important determinant of morbidity and mortality. The original treatment strategy sought to reverse mechanical changes: e.g. reducing pre- and after- as well as volume load. Angiotensin-converting enzyme inhibitors are now a universal therapy for all forms of HFrEF. Independent of loading conditions, other pathophysiologic mechanisms like inflammation, metabolism, and fibrosis also contribute to adverse LV remodelling. Therefore, developing innovative drugs will depend on meticulously identifying novel targets beyond, taking into account that there may be large inter-individual differences regarding pathophysiologic mechanisms. In the above-mentioned CANTOS trial, pre-selecting patients based on CRP was key to success. Consequently, we recommend elucidating surrogate 'biomarkers' that indicate the pathomechanisms of LV remodelling. As circulating biomarkers reflect systemic changes but are not cardio-specific, novel imaging modalities might help reveal myocardial mechanisms and facilitate pathophysiologically guided individualized treatment (*Graphical abstract*).

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