Reverse remodelling and myocardial recovery in heart failure

Gene H. Kim[1], Nir Uriel[1] and Daniel Burkhoff[2]

Abstract | Advances in medical and device therapies have demonstrated the capacity of the heart to reverse the failing phenotype. The development of normative changes to ventricular size and function led to the concept of reverse remodelling. Among heart failure therapies, durable mechanical circulatory support is most consistently associated with the largest degree of reverse remodelling. Accordingly, research to analyse human tissue after a period of mechanical circulatory support continues to yield a wealth of information. In this Review, we summarize the latest findings on reverse remodelling and myocardial recovery. Accumulating evidence shows that the molecular changes associated with heart failure, in particular in the transcriptome, metabalome, and extracellular matrix, persist in the reverse-remodelled myocardium despite apparent normalization of macrolevel properties. Therefore, reverse remodelling should be distinguished from true myocardial recovery, in which a failing heart regains both normal function and molecular makeup. These findings have implications for future research to develop therapies to repair fully the failing myocardium. Meanwhile, recognition by society guidelines of this new clinical phenotype, which is coming to be known as a state of heart failure remission, underscores the need to accurately define and identify reverse modelled myocardium for the establishment of appropriate therapies.

The term left ventricular (LV) remodelling describes alterations in the global geometric, cellular, and extracellular composition of the left ventricle in response to the mechanical stress and neurohormonal activation that occur in heart failure. The initial remodelling concepts were introduced in reports describing ventricular dilatation and myocyte changes after myocardial infarction in rats[1] and humans[2]. Subsequently, Pfeffer *et al.* introduced the fundamental concept that the structural aspects of remodelling are defined and quantified by shifts of the ventricular end-diastolic pressure–volume relationship (EDPVR)[3] (FIG. 1a), a finding that was soon confirmed in human end-stage failing hearts obtained at the time of heart transplantation[4] (FIG. 1b). These shifts of the EDPVR, which result from changes in myocyte length, width, and organization, are associated with a multitude of cellular, molecular, and extracellular changes that have been reviewed previously[5].

Although the remodelled left ventricle was initially considered to be irreversibly enlarged and dysfunctional, clinical studies in the past 22 years have shown that heart size can decrease to a certain extent with the use of drug therapies, particularly angiotensin-converting enzyme (ACE) inhibitors and β-blockers, and with cardiac resynchronization therapy (CRT)[6]. However, studies of human hearts explanted from transplantation recipients after a period of mechanical circulatory support with LV assist devices (LVADs) showed for the first time that the EDPVR of human end-stage failing hearts can substantially shift back to normal values[7] (FIG. 1c). Such studies allowed for definitive differentiation between LV size reduction owing to decreased preload along a fixed EDPVR (that is, unloading) and shifts of the EDPVR back to normal values (FIG. 1d). The observations from this study led us to introduce the term 'reverse remodelling' (REF. 7).

Reverse remodelling has been the focus of several reviews[6,8,9]. In the context of the current broader understanding of remodelling, ventricular reverse remodelling refers to the restoration of more-normal cell size and chamber geometry, resulting in a leftward shift of the EDPVR towards normal values, and is associated with many beneficial changes in molecular, metabolic, and extracellular matrix (ECM) properties of the myocardium[6,8,9]. Importantly, the observation that reverse remodelling is also associated with markedly improved myocyte and chamber contractility generated investigations to understand the degree of normal function that end-stage failing hearts can recover. However, just as these early studies of reverse remodelling and myocardial recovery were generating enthusiasm and hope

[1]*Department of Medicine, Division of Cardiology, University of Chicago, 5841 S. Maryland Avenue, Chicago, Illinois 60637, USA.*
[2]*Cardiovascular Research Foundation and Division of Cardiology, Columbia University Medical Center/ New York-Presbyterian Hospital, 1900 Broadway 9th Floor, New York, New York 10019, USA.*

Correspondence to D.B.
dburkhoff@crf.org

doi:10.1038/nrcardio.2017.139
Published online 21 Sep 2017

Key points

- Reverse remodelling is the process by which failing myocardium demonstrates normative changes in chamber geometry and function, and might also include correction of molecular and transcriptional abnormalities
- Advances in sequencing technologies have allowed for detailed analysis of transcriptome changes in the setting of reverse remodelling, including non-coding RNAs such as microRNAs and long non-coding RNAs
- Despite evidence of reverse remodelling, numerous abnormalities in myocardial transcriptome, metabolism, and extracellular matrix persist, supporting the concept that myocardial remission is distinct from myocardial recovery
- The newly proposed phenotype of 'heart failure with improved ejection fraction' highlights the clinical course of 'remission' with relapses in heart failure symptoms despite improvement in ventricular structure and function

for possibly 'curing' heart failure, findings from studies in animal models and human tissues raised the question of whether true myocardial recovery is possible[10,11].

Studies of paired human myocardial tissue samples obtained from the same patient at LVAD implantation and subsequent transplantation offered a new, human-tissue-based experimental model for studying heart failure and the changes associated with its reversal. The data obtained from these studies increased our understanding of some of the biological and physiological determinants and obstacles to achieving full reverse remodelling and recovery[11]. Despite this new stream of data, substantial knowledge gaps remain owing to the limited availability and heterogeneity of human-tissue studies. Accordingly, investigators have turned to animal models, which provide experimental flexibility and control over extraneous factors, such as varied disease substrates and background medical therapy.

In this Review, we summarize the latest information on reverse remodelling and myocardial recovery, which is largely on the transcriptional and metabolomic changes and the alterations in the ECM that occur during reverse remodelling. Of note, the most informative data on reverse remodelling are derived from studies in the setting of LVAD support. Less information is available on reverse remodelling in response to other therapies for several reasons. First, tissue samples related to nonsurgical therapies are generally not readily available. Some studies have relied on right heart biopsies, but the type and number of assays that can be performed on such samples are limited. Second, the degree of reverse remodelling is extremely variable in response to drug, valve, revascularization, and resynchronization therapies for heart failure. Some patients might not have any reverse remodelling, whereas other patients can have substantial reverse remodelling. This heterogeneity contrasts with a consistent reverse structural remodelling with LVAD support, as evidenced by the consistent leftward, time-dependent shift of the EDPVR[12]. However, as noted above, reverse remodelling has also been observed with the use of medical therapies and CRT; therefore, in this Review, in addition to studies in the setting of LVAD support, information derived from the small number of studies in other therapies, such as mitral valve repair or replacement, is also discussed. Results from human studies and, when appropriate, animal models are included.

Transcriptome
The part of the genetic code that is transcribed into mRNA molecules; reflects the genes that are being actively expressed at any given time.

Mechanical unloading
The reduction of ventricular end-diastolic volume and pressure (preload), peak systolic pressure generation (afterload pressure), and overall myocardial oxygen demand; unloading is provided by ventricular assist devices that pump blood from the left ventricle to the arterial system, or by other forms of mechanical circulatory support.

Mechanisms of reverse remodelling

The factors that drive remodelling can be divided into two broad categories: mechanical stress and biochemical stress owing to abnormal circulating and local neurohormonal and cytokine factors. These stress signals lead to cardiomyocyte hypertrophy, apoptosis, and a reduction in contractile strength, with profound effects on gene expression, protein function, signalling pathways, metabolic processes, and electrophysiological properties (BOX 1). These stress signals also induce extensive changes in the ECM and myocardial fibroblast properties. Comparisons of the effects of LVAD support on LV and right ventricular (RV) chamber and tissue properties has helped to identify factors that are regulated by the two different drivers of reverse remodelling[13]. Properties with different reverse remodelling in the left and right ventricle are more likely to be regulated by reductions in mechanical stress. Conversely, because LV and RV myocardium are perfused by the same blood, properties with similar reverse remodelling in both chambers are more likely to be mediated by circulating factors that normalize during LVAD support[14]. These findings indicate that chamber specificity and sampling location must be taken into account in studies of reverse remodelling.

Changes in gene expression. Several studies have demonstrated, to varying degrees, that in the reverse-remodelled ventricle, many of the cellular features of the remodelled myocardium might return closer to a nonfailing phenotype. Early studies identified the so-called 'fetal-like' gene expression profile associated with the onset of cardiac pathology[15]. However, gene-expression profiles revealing aetiology and a corresponding signature of normalization have not been found[9]. Additionally, as the field of transcriptomics has advanced, the complexity of the transcriptional landscape has increased.

In 2005, a transcriptome analysis of 199 human myocardial samples from failing, nonfailing, and mechanically unloaded hearts showed significant heart-failure-related changes in the expression of >3,000 genes[16]; however, mechanical unloading did not induce a generalized 'transcriptional recovery', with only 5% of those genes showing normalization of expression levels after LVAD support[16]. In addition, a new subset of genes was dysregulated in the reverse-remodelled, LVAD-supported heart compared with normal myocardium[16]. These findings indicate that abnormal gene-expression changes persist despite the normal appearance of ventricular function achieved with mechanical unloading. Furthermore, new 'reverse remodelling genes' are dysregulated; the function of these latter genes in the reverse-remodelling process is unknown.

Other studies have had similar conclusions, although more attention has been paid to delineating the specific gene classes that are upregulated and downregulated, such as changes in genes associated with integrin signalling pathways[17], and in genes encoding sarcomeric and cytoskeletal proteins[18]. Although such studies shed light on gene-expression changes in the setting of reverse remodelling, the small study sizes limit the generalizability of the identified pathways to the understanding

Epigenetic
The study of changes in organisms caused by modification of gene expression rather than alteration of the genetic code itself.

of heart recovery. In an effort to examine the reported gene-expression changes across varying studies, Ton *et al.* reviewed eight studies in patients with heart failure that included myocardial gene-expression data before and after LVAD support. The analysis included 2003–2014 studies that had different gene-expression platforms and patient populations, to find common gene-expression changes across these methodological differences. Interestingly, the investigators found that immune-modulation pathways, particularly pathways involving tumour necrosis factor, the PIK3–AKT signalling pathway, and metallothionine-mediated antioxidant effects emerged as common findings[19], which echoes the concept of immune responses as mediators of cardiac injury and repair[20].

Just as animal models of heart failure guided the study of failing myocardium, animal models continue to provide a valuable roadmap for reverse remodelling and recovery. Expanding on previous findings[16], a study in a transgenic mouse model of reversible dilated cardiomyopathy, with characterization of transcriptional and epigenetic changes in the myocardium during the failing and recovering phases, showed that improvements in LV structure and function are not simply a matter of reversing dysregulated gene expression[21]. LV structural and functional improvements were accompanied by a new set of expressed genes related to the ECM, cytoskeleton, sarcomere, and excitation–contraction coupling[21], highlighting a shifting transcriptomic landscape distinct from

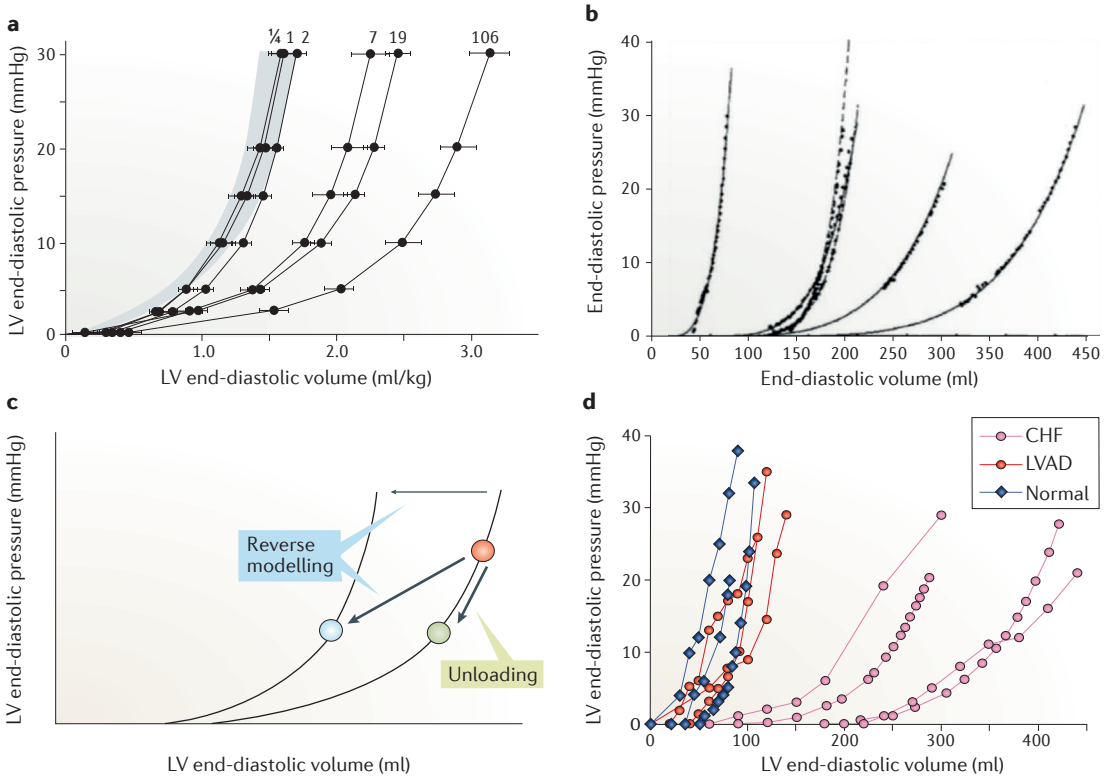


Figure 1 | **Ventricular end-diastolic pressure–volume relationship curves. a** | End-diastolic pressure–volume relationship (EDPVR) in rat models of myocardial infarction (MI) and subsequent ventricular remodelling. Shaded area shows the range of normal EDPVR; each curve represents the EDPVR measured at the specified day after MI, delineating the time course of heart remodelling[3]. **b** | First *ex vivo* measurements of EDPVRs in human failing hearts obtained at the time of heart transplantation. Each curve represents data from a different heart: the left-most curve (with small end-diastolic volumes) is from a patient with restrictive cardiomyopathy; the other curves are from patients with dilated and ischaemic cardiomyopathies, and reflect hearts with various degrees of enlargement (that is, remodelling)[4]. **c** | Comparison of changes in left ventricular (LV) end-diastolic volume and pressure owing to acute unloading (LV end-diastolic pressure–volume values move along a fixed EDPVR from the red to the green point) with changes during reverse remodelling, as occurs during chronic ventricular unloading (LV end-diastolic pressure and volume decrease, but the EDPVR also shifts, moving from the red to the blue point). Therefore, differentiating reverse remodelling from pressure and volume reductions owing to LV unloading generally requires an assessment of EDPVR shifts[7]. **d** | EDPVRs of *ex vivo* hearts obtained at heart transplantation from four patients with end-stage idiopathic cardiomyopathy without LV assist device (LVAD) support (CHF), three patients with heart failure after prolonged LVAD support (LVAD), and three individuals with nonfailing hearts (Normal). EDPVRs of nonsupported hearts are right-shifted to larger volumes, indicative of remodelling, whereas EDPVRs of LVAD-supported hearts are similar to those of the normal hearts even though at the time of LVAD implantation, the hearts were dilated to a similar degree as the nonsupported hearts. The term 'reverse remodelling' was introduced based on these findings. Data for the graph was obtained from REF. 7. Panel **a** is reproduced from Pfeffer, J. M. *et al.* Progressive ventricular remodeling in rat with myocardial infarction. *Am. J. Physiol.* **260**, H1406–H1414 (1991), with permission from the American Physiological Society. Panel **b** is reproduced from Burkhoff, D. *et al.* In vitro studies of isolated supported human hearts. *Heart Vessels* **4**, 185–196 (1988), with permission from Springer Nature.

Box 1 | **Future research directions**

Changes during reverse remodelling

Available evidence shows that reverse remodelling is associated with cellular and molecular changes (see figure):

- Decrease in cardiac myocyte size
- Restoration of expression levels of genes related to excitation–contraction coupling towards levels of a nonfailing heart
- Reduction in total collagen content with haemodynamic unloading and angiotensin-converting enzyme inhibitor therapy
- Increased myocardial microvascular density with haemodynamic unloading
- Reversal of the abnormal fetal gene programme towards a gene programme of a nonfailing heart

Myocardial recovery

The progression from reverse remodelling to true myocardial recovery needs to demonstrate recovery at the clinical level, including:

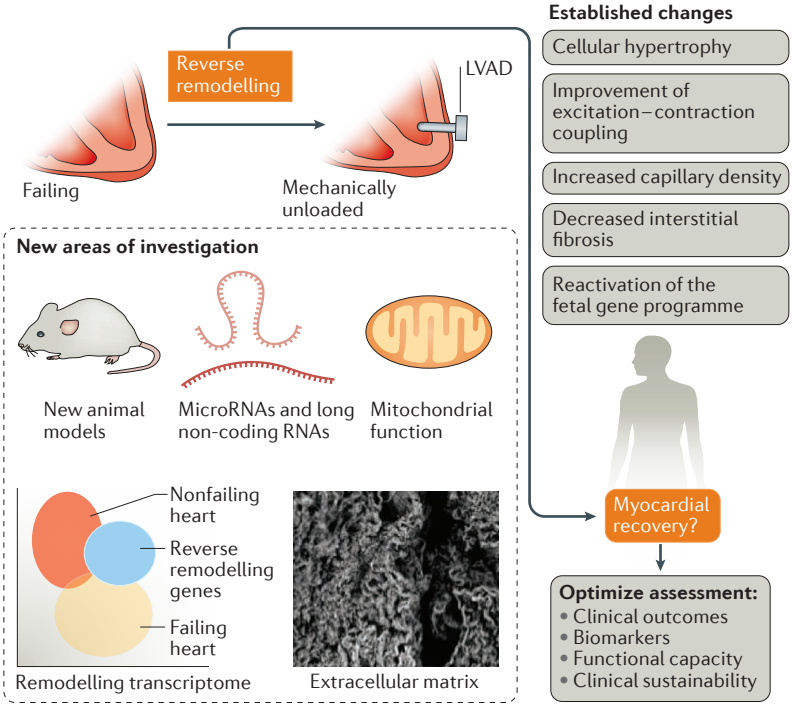
- A sustained clinical response with a decrease in long-term morbidity and mortality to match rates in individuals with nonfailing hearts
- Restoration in cardiac biomarkers indicative of myocardial recovery
- Restoration of exercise capacity

New areas of investigation

- Continue to develop animal models of myocardial recovery to define more precisely the molecular and cellular changes observed in human myocardial tissue, in particular, to explore the transcriptional changes in the setting of reverse remodelling (see figure)
- Investigate the changes in mitochondrial structure and function in individuals who have myocardial reverse remodelling and possible recovery
- Understand the changes in the extracellular matrix, incorporating the 3D structure and non-collagen protein changes in addition to the fibrillar component, as a means to study myocardial stiffness and changes in myocardial recovery

Optimize assessment of myocardial reverse remodelling and recovery

- Define the metrics to assess the varying degrees of myocardial recovery, in particular in the setting of left ventricular assist device support, to quantify myocardial recovery
- Develop noninvasive imaging modalities to aid in the quantification of myocardial recovery in the setting of medical or device therapy
- Establish collaborative research networks to provide paired human tissue samples with standardized metrics for assessment of myocardial reverse remodelling and recovery
- Explore the relative contribution of genetic factors, extracellular matrix, and mitochondria in the determination of reverse remodelling and recovery



both the end-stage failing myocardium and the normal myocardium. This transgenic model of reversible dilated cardiomyopathy also allowed examination of the capacity of the reverse-remodelled heart to withstand a second haemodynamic stress, which was achieved with pressure overload via transaortic constriction[21]. As more of the heart-failure-related gene programme returned to normal values, the hearts had a greater capacity to withstand this second haemodynamic stress. Linking these findings to human biology, this result provides a plausible molecular-based hypothesis for why patients who had previously 'recovered' (discussed further below) can have a recurrence of heart failure and might indeed be vulnerable to recurrent clinical events, owing to re-emergence of heart-failure-associated transcriptional abnormalities.

Although this early work generated important and intriguing results, the genomic coverage provided in most, if not all, of these studies was limited by the use of conventional microarray or polymerase chain reaction-based assays, which cannot provide a detailed picture of the myocardial transcriptional landscape. In the past 15 years, the expansion of technology, bioinformatic resources, and scalability of next-generation platforms have simultaneously provided more in-depth and expansive coverage of the transcriptome landscape. For example, the development of next-generation sequencing enabled more precise and comprehensive study of the global molecular changes occurring in the failing and recovering heart. Importantly, in addition to protein-coding RNA, non-coding RNAs can have major roles in the regulation of gene expression at the transcriptional and translational levels. These non-coding transcripts are categorized into small non-coding RNAs, including microRNAs (miRNAs), and long non-coding RNAs (lncRNAs).

MicroRNAs. MiRNAs are crucial components in multiple facets of stress responses in the heart. Bound to the RNA-induced silencing complex, these short, non-coding RNAs can promote mRNA degradation or inhibit protein translation. Cardiac miRNAs are regulated by haemodynamic stress and have been shown to recapitulate the features of the failing heart in animal models[22]. Early studies of miRNAs in reverse remodelling have

Next-generation sequencing
High-throughput DNA-sequencing technologies in which millions of DNA strands can be sequenced in parallel, yielding substantially more throughput and minimizing the need for the fragment-cloning methods compared with previous methods.

yielded varied results. One study found 28 miRNAs upregulated in failing myocardial samples that normalized after LVAD support, in contrast to the mRNA signature of failing myocardium, which was largely unchanged with mechanical unloading[23]. However, a limitation of this study is that the comparisons were made between unpaired tissue samples from different patients; we have previously emphasized the potential differences in conclusions derived from molecular studies comparing paired and nonpaired samples[24]. Interestingly, a study published in 2014 that included paired samples showed that miRNA expression did not change significantly in response to mechanical unloading[25]. Beyond paired tissue samples, differences in methodology, small sample sizes, and different patient populations might have contributed to the different results between these studies.

To analyse specifically the role of miRNAs in myocardial recovery, Ramani *et al.* examined the myocardial miRNA expression pattern in 14 patients who had LV recovery and underwent LVAD removal and 14 patients on LVAD support with no evidence of recovery[26]. Interestingly, four miRNAs (miR-15b, miR-23a, miR-26a, and miR-195) had lower expression levels at the time of LVAD implantation in the LV-recovery group compared with the LVAD-dependent group[26]. In a small validation cohort ($n = 7$), expression levels of miR-23a and miR-195 at the time of LVAD implantation were also lower in those patients that had the LVAD explanted[26]. Interestingly, the expression levels of these miRNAs were unchanged after the period of LVAD support. In addition, miR-23a and miR-195 levels were similar in LV-recovery and nonfailing myocardial samples[26], suggesting that these miRNAs might be a reflection of the severity of heart failure at the time of LVAD implantation, rather than a marker of reverse remodelling or recoverability.

The use of serum miRNA signatures as a biomarker for ventricular function has also been explored. A study to assess miRNA expression profiles in both myocardial tissue and serum in healthy individuals, in patients with stable heart failure, and in patients with advanced heart failure undergoing LVAD implantation showed that in the first two groups, <0.1% of all circulating miRNAs were cardiac-specific miRNAs[27]. However, in patients with advanced heart failure undergoing LVAD implantation, serum levels of the cardiac-specific miRNAs miR-208a, miR-208b, and miR-499, and the muscle-specific miRNAs miR-1-1 and mir-133b, increased by 140-fold[27]. During the period of LVAD support (at 3 and 6 months after LVAD implantation) serum levels of these miRNAs decreased to nearly normal levels. Whether this miRNA signature is a reflection of mechanical unloading or simply a marker of myocardial injury remains unanswered. Further studies of circulating miRNA expression patterns with rigorous assessment of reverse remodelling are warranted. Understanding whether miRNA expression patterns can normalize with reverse remodelling is important in the field of myocardial recovery. Owing to the large biological effect that even a single miRNA can induce, a persistently dysregulated state can easily affect the capacity of the failing myocardium to achieve recovery.

Long non-coding RNAs. LncRNAs are a heterogeneous group of non-coding RNA transcripts containing >200 nucleotides, located within or between protein-coding genes. LncRNAs can regulate gene expression at different levels — on mRNAs, as epigenetic modifiers of chromatin structure, forming molecular scaffolds for the assembly of macromolecular complexes, or directly interacting with proteins[28]. Not surprisingly, altered expression of lncRNAs has been shown in murine models of heart failure and has been linked to adverse remodelling in heart failure in humans[29–31].

A comprehensive deep-sequencing analysis, albeit in a small study population (16 paired tissue samples of failing myocardium before and after LVAD support), of non-coding RNA expression patterns showed that lncRNAs had the most dynamic expression changes in response to haemodynamic unloading with an LVAD[25]. Expression levels of both mRNAs and miRNAs did not normalize[25], again emphasizing the persistently abnormal transcriptional state of the reverse-remodelled heart. Although limited by the cohort size, the comprehensive profiling used in this study, which had not been used previously in human failing myocardial samples, uncovered a surprisingly large number of lncRNAs (nearly 18,000) differentially expressed in human failing myocardium, emphasizing the complexity of the transcriptome. Although the lncRNA profile changed after LVAD support, the specific lncRNAs that changed expression and their functional importance is unknown.

As the transcriptional landscape continues to evolve, the role of lncRNAs and other non-coding RNAs in the pathogenesis of cardiomyopathies and their contribution to reverse LV remodelling remains under investigation. The diversity of function and targets that make non-coding RNAs powerful regulators of disease also confound the precise study of their function in disease states. This layer of gene regulation underpins the sophisticated regulatory networks not only coordinating physiological responses, but also pathophysiological responses in the failing heart. From these studies, a unifying emerging theme is the persistence of transcriptional abnormalities in protein-coding and non-coding RNAs in the reverse-remodelled heart. However, these studies also reveal new gene-expression patterns as normative changes to the heart, potentially opening new avenues for gene discovery and development of novel therapeutic strategies.

Metabolic changes during reverse remodelling. The study of the metabolome has expanded owing to innovative developments in informatics and analytical technologies that enable higher molecule resolution, thereby providing a more complete metabolic profile than with previous methodologies. In healthy adult cardiomyocytes, the major energy source for the heart is fatty acid β-oxidation in the mitochondria. Early observations showed an impaired capacity of the mitochondria in failing myocardium to oxidize fatty acids, along with an increase in glycolysis that is uncoupled from glucose oxidation[32] (FIG. 2). Although in the setting of reverse remodelling β-blockade can shift cardiac metabolism

Metabolome
Metabolites within cells, fluids, and tissues, and their interactions within a biological system, which directly reflect the underlying biochemical activity and state of cells and tissues.

Fatty acid β-oxidation
Process by which fatty acid molecules are broken down in the mitochondria to generate acetyl-CoA, which enters the Krebs cycle, and NADH and $FADH_2$, co-enzymes used in the electron transport chain.

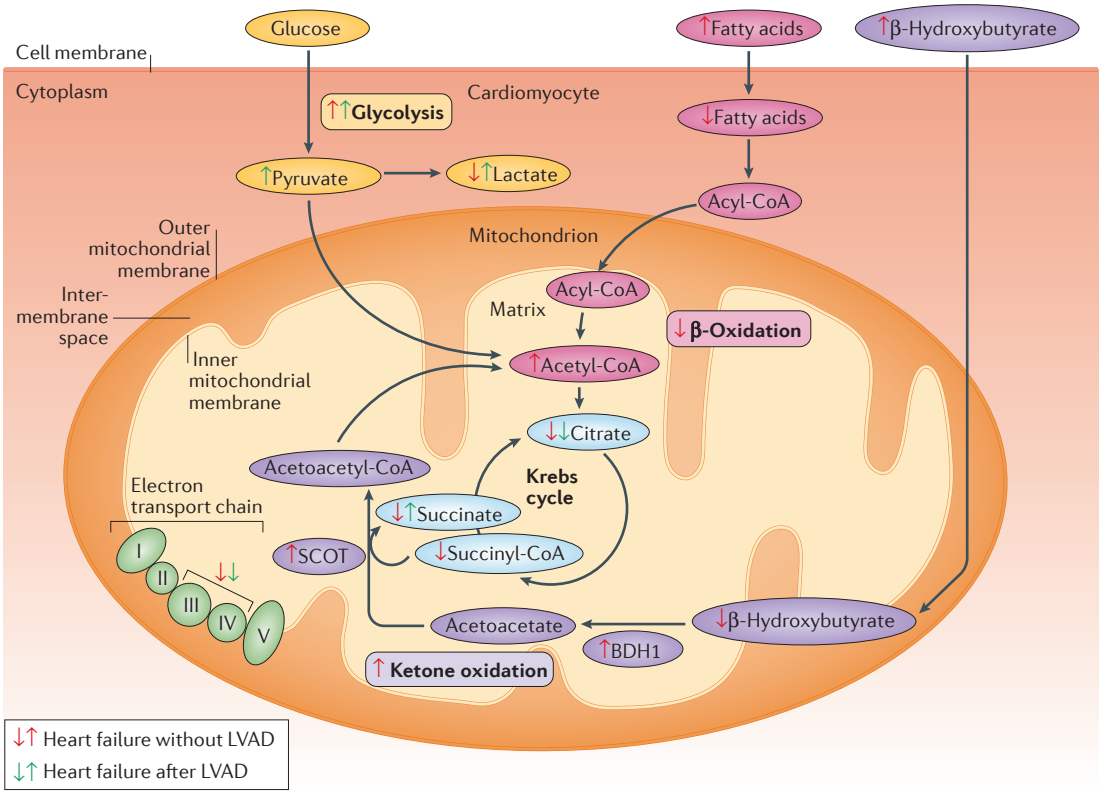


Figure 2 | **Metabolic shift in heart failure.** In advanced heart failure, cardiomyocyte fatty acid uptake and β-oxidation, which in the healthy adult heart generates most of the cardiac ATP, and the oxidative function of mitochondria decrease. In failing myocardium, the electron transport chain has significantly lower respiration capacity compared with normal hearts, and the mitochondrial oxidative capacity remains reduced after left ventricular assist device (LVAD) unloading[37]. In the failing heart, the predominant fuel source shifts from mitochondrial fatty acid oxidation towards glycolytic pathways. The increased glycolysis remains elevated after LVAD support, which together with the defect in mitochondrial oxidation leads to increased cytosolic lactate rather than the increased pyruvate that enters the Krebs cycle. In patients with advanced heart failure, elevations in the serum concentration of ketone bodies (such as β-hydroxybutyrate) are accompanied by alterations in metabolites, such as increased levels of acetoacetate and acetoacetyl-CoA, and enzymes, such as increased expression levels of genes coding for the enzymes implicated in ketone oxidation D-β-hydroxybutyrate dehydrogenase (BDH1) and succinyl-CoA:3-oxoacid-CoA transferase (SCOT), consistent with the upregulation of the ketone oxidation pathway in the heart[35,36].

towards increased glucose metabolism[33], more detailed data on metabolic changes in the setting of reverse remodelling are lacking.

Past research has focused primarily on myocardial use of glucose and fatty acids; however, work in the past 3 decades has shown that the heart can oxidize other substrates such as lactate, ketone bodies, and amino acids[34]. Increased ketone oxidation has been documented in animal and human failing heart tissue[35,36]. Enzymes regulating ketone metabolism were upregulated, whereas those regulating glucose and fatty acid metabolism were downregulated in failing myocardium compared with nonfailing myocardium[35,36] (FIG. 2).

In contrast to the failing heart, the metabolic adaptations in the setting of mechanical unloading and reverse remodelling have been studied only in the past 20 years. Consistent with the findings in failing hearts[35,36], a study to characterize the metabolic phenotype from paired myocardial tissue samples obtained before and after LVAD implantation showed that the failing myocardium before LVAD implantation had reduced levels of glucose-1-phosphate and glucose-6-phosphate, a signature of decreased glucose utilization[37]. After mechanical unloading, glycolysis increased, but oxidative metabolism did not change significantly, as demonstrated by high levels of pyruvate and lactate in the unloaded myocardium[37] (FIG. 2). Despite mechanical unloading with LVAD therapy, Krebs cycle abnormalities persisted, as shown by a decreased succinyl-CoA-to-acetyl-CoA ratio[37]. To understand the upregulation of glycolysis in the absence of upregulation in mitochondrial oxidative metabolism, the investigators examined the changes in mitochondrial structure and function, and demonstrated a decrease in mitochondrial volume density in the failing myocardium, as assessed by electron microscopy and relative mitochondrial DNA content[37]. Mitochondrial oxidative capacity was low, and did not improve with mechanical unloading[37] (FIG. 2). Interestingly, within a small subgroup of patients who had substantial reverse remodelling, the improvement in both mitochondrial function and structure was more pronounced than in patients with no reverse remodelling.

Ketone bodies
Water-soluble molecules produced by the liver from fatty acids during gluconeogenesis, including acetoacetate, β-hydroxybutyrate, and acetone.

Matrix metalloproteinases
Enzymes that can break down proteins of the extracellular matrix, such as collagen, and other proteins residing on the cell surface or within the matrix.

These studies highlight the possibility of using the metabolic adaptations of the failing myocardium in myocardial recovery protocols, but again emphasize another aspect — reverse remodelled hearts continue to have abnormal features, in this case within the mitochondria. As such, continuing the investigation into the metabolic profile of progressive heart failure and how these profiles evolve in the setting of reverse remodelling and recovery is important.

Changes in the extracellular matrix. The ECM has a variety of functions: providing structural support[38,39], being a reservoir for growth factors and cytokines, providing a path for transportation of different molecules, and facilitating intercellular communication. Changes in composition, structure, and cellular interactions in the ECM provide a critical adaptation to haemodynamic and neurohormonal stress[40] (FIG. 3). In reverse remodelling, especially in the context of LVAD support, changes in ECM are the result of a complex interplay between disease aetiology affecting matrix composition, changes in ventricular wall stress, changes in enzyme activities, changes in neurohormonal milieu, and use of medical therapies, all of which can influence ECM turnover and stability.

With regard to the structural function of the ECM in the context of failing and reverse-remodelled myocardium, collagen content has received most of the attention. Nevertheless, the available data are conflicting on whether collagen content is increased or decreased during LVAD support (TABLE 1). However, ACE inhibitor therapy was shown to have a major effect on collagen synthesis[41]. Total collagen and crosslinked collagen increased in patients with LVAD support who were not taking an ACE inhibitor, whereas both collagen parameters decreased towards normal levels in those patients taking an ACE inhibitor[41]. Interestingly, changes in directly-measured myocardial stiffness paralleled the changes in crosslinked collagen content. This study is noteworthy not only because it was the first demonstration of the interaction between LVAD-induced and drug-induced reverse remodelling, but because this study highlighted that background medical therapy (which is uncontrolled in observational studies) in patients supported with mechanical circulatory devices can influence study findings and conclusions.

The expansion of the ECM via deposition of collagen and the regulators of collagen deposition have received considerable attention in the study of remodelling in heart failure. Animal and human studies have shown that matrix metalloproteinases (MMPs) and their endogenous inhibitors, tissue inhibitors of metalloproteinases (TIMPs), have a dynamic range of expression depending on the severity of the hypertrophic stimuli, ischaemia, or infarction, and these changes contribute to cardiac remodelling as the ventricle dilates and declines in function. LV myocardial MMP activity increases by more than twofold with both nonischaemic and ischaemic dilated cardiomyopathy compared with nonfailing hearts, with selective upregulation of specific MMP isoforms[42]. By contrast, TIMP expression and activity is decreased in heart failure[43]. These seemingly coordinated changes favour breakdown of the collagen matrix, a factor that might underlie the unfavourable myocyte reorganization during remodelling.

Changes in MMPs and TIMPs in the setting of reverse remodelling and recovery have not been extensively studied. One study showed that MMP and TIMP levels did not reverse to nonfailing levels after mechanical unloading alone[44], but that MMPs are decreased and TIMPs are increased during unloading with concomitant use of ACE inhibitors[41] (FIG. 3c).

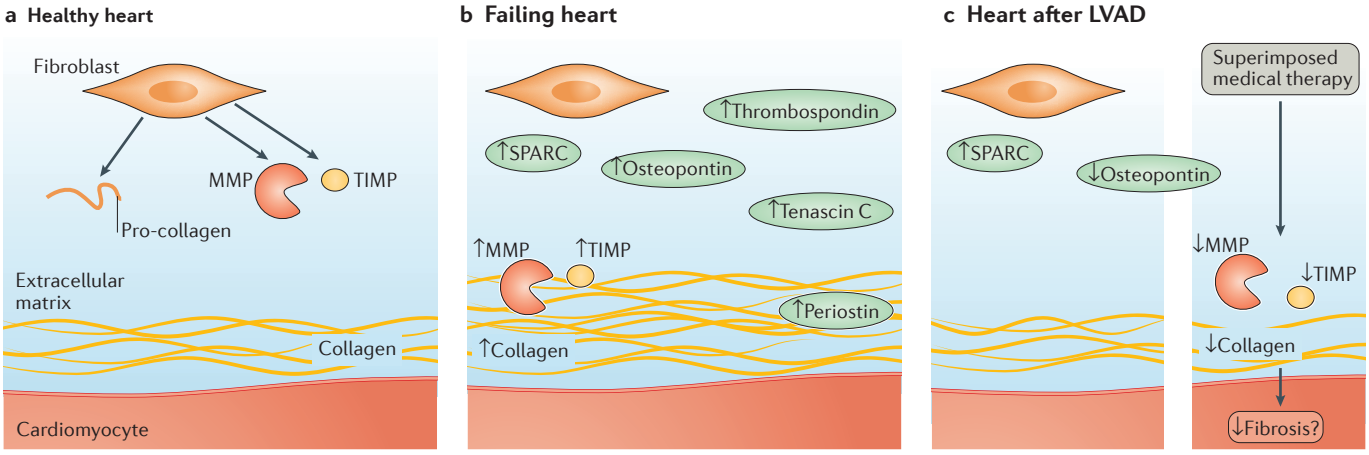


Figure 3 | **Altered extracellular matrix. a** | Schematic diagram of the myocardial extracellular matrix and associated proteins. **b** | In the failing myocardium, the levels of matrix metalloproteinases (MMP) are increased, whereas the levels of their endogenous inhibitors, tissue inhibitors of metalloproteinases (TIMPs), decrease, and the levels of matricellular proteins including osteopontin and SPARC (also known as osteonectin), are also elevated. Collagen content increases as a result of changes in the expression of genes encoding proteins associated with a profibrotic phenotype, such as collagen, fibronectin, and tumour necrosis factor, in cardiac fibroblasts. **c** | In failing myocardium with left ventricular assist device (LVAD) support, medical therapy with angiotensin-converting enzyme inhibitors might improve the MMP/TIMP ratio and reduce myocardial collagen content. Matricellular proteins such as osteopontin return to normal levels, but SPARC levels remain elevated[44], with partially preserved collagen organization and extracellular matrix–myocyte interaction.

Beyond its structural function, the ECM can influence extracellular cytokines and signalling proteins and their communication to cells, largely via the matricellular proteins. Matricellular proteins — including osteopontin, SPARC (also known as osteonectin), thrombospondins, tenascin, and periostin — interact with cell-surface receptors, growth factors, and other ECM proteins, and function as a link between ECM proteins to modulate cell behaviour[45]. Importantly, the levels of matricellular proteins increase in response to stress[45]. Mechanical unloading with an LVAD was shown to restore the fibrillar ECM, osteopontin levels, and the basement membrane; however, regulators of collagen processing such as SPARC (which binds to pro-collagen, participating in processing and assembly of mature, crosslinked collagen fibrils) remained elevated[44]. Therefore, beyond the changes in the fibrillar content, abnormalities of non-fibrillar ECM components persist after LVAD-induced

Table 1 | **Molecular changes with left ventricular assist device support**

Study	Evidence for reverse remodelling	Aetiology*	Design‡	Findings	Refs
Collagen and fibrillar component					
Maybaum *et al.* (2007)	Echocardiography	Mixed	Paired tissue samples	Decreased total collagen deposition after LVAD support	90
Bruggink *et al.* (2006)	Not assessed	Mixed	Paired tissue samples	Early increase in ECM volume, with reduction in ECM volume with longer LVAD support	91
Klotz *et al.* (2007)	Not assessed	Mixed	Paired tissue samples	Combination of angiotensin-converting enzyme inhibitor with LVAD therapy reduced myocardial collagen content	41
Extracellular matrix turnover					
Klotz *et al.* (2007)	Not assessed	Mixed	Paired tissue samples	MMP1/TIMP1 ratio normalization with angiotensin-converting enzyme inhibitor therapy	41
Sakamuri *et al.* (2016)	Not assessed	Nonischaemic	Samples from failing, LVAD-supported, and healthy hearts	Persistent elevation in SPARC levels after LVAD	44
Gene expression					
Hall *et al.* (2004)	LVAD explantation owing to recovery	Mixed	Paired tissue samples	Mechanical unloading induced significant expression changes in genes related to vascular signalling	17
Margullies *et al.* (2005)	Isolated myocyte dimensions	Mixed	Samples from failing, LVAD-supported, and healthy hearts (nonpaired samples)	Only 5% of genes associated with heart failure had normal expression levels after LVAD	16
Birks *et al.* (2005)	LVAD explantation owing to recovery	Nonischaemic	Paired tissue samples	Recovered hearts had significant expression changes in genes encoding sarcomeric and cytoskeletal proteins	18
Ton *et al.* (2016)	Mixed	Mixed	Meta-analysis	LVAD support altered immune-modulation pathways	19
Long non-coding RNAs					
Yang *et al.* (2014)	Not assessed	Mixed	Paired tissue samples	LVAD support induced expression changes in long non-coding RNAs	25
MicroRNAs					
Matkovich *et al.* (2009)	Not assessed	Mixed	Samples from failing, LVAD-supported, and healthy hearts (nonpaired samples)	Normalization of microRNA signature after LVAD	23
Ramini *et al.* (2011)	LVAD explantation owing to recovery	Nonischaemic	Paired and nonpaired tissue samples	Differential expression of miR-23 and miR-195 in the recovered myocardium	26
Akat *et al.* (2014)	Not assessed	Mixed	Paired tissue samples	Marginal differences myocardial microRNA levels before and after LVAD support	27
Yang *et al.* (2014)	Not assessed	Mixed	Paired tissue samples	Marginal differences in myocardial microRNA levels before and after LVAD support	25
Mitochondria					
Bedi *et al.* (2016)	Not assessed	Nonischaemic	Samples from failing hearts and paired heart samples	LVAD support induced an increase in expression of genes encoding enzymes involved in ketone oxidation	36
Diakos *et al.* (2016)	Echocardiography, right heart catheterization after LVAD	Mixed	Paired heart samples	Abnormal mitochondrial morphology persistent after LVAD, with no change in oxidative metabolism; persistent increase in glycolysis after LVAD	37

*Nonischaemic or ischaemic cardiomyopathy. ‡Paired samples collected at LVAD implantation and explantation/transplantation. ECM, extracellular matrix; LVAD, left ventricular assist device; MMP, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinase.

reverse remodelling (FIG. 3). Furthermore, MMPs and matricellular proteins can also degrade nonfibrillar components, such as cytokines and growth factors present in the ECM[46]. Therefore, the changes induced by reverse remodelling, or lack thereof, in these nonfibrillar components of the ECM can have consequences in the myocardium beyond collagen and its turnover.

In summary, the biochemical, structural, and functional roles of ECM changes remain the most poorly understood aspect of heart remodelling and reverse remodelling. Future studies must consider the confounding factors in previous studies of human tissues, including variability in background medical therapy and disease substrate, and need to address the independent roles of mechanical load, regulation of tissue hormone levels, and enzymatic regulation of ECM in these processes. Furthermore, beyond ECM composition, alterations in the 3D organization and functional mechanical properties have not been investigated in the setting of reverse remodelling.

Therapies to induce reverse remodelling

A number of therapies in addition to LVADs have been shown to induce reverse remodelling. As reviewed in detail previously[6], numerous clinical studies have shown that ACE inhibitors[47], mineralocorticoid-receptor antagonists[48], and β-blockers[49,50] promote reverse remodelling, as shown by reductions of LV volume and mass, restoration of a more normal ventricle geometry, and improved LV ejection fraction (LVEF). These changes are consistently associated with reductions in morbidity and mortality[6]; so much so that some investigators have advocated that the reduction in LV volume can serve as a valid surrogate end point for clinical outcomes in studies of new therapies. Similarly, CRT has been shown to reduce morbidity and mortality[51,52] and affect reverse remodelling[53,54], as shown by decreases in systolic and diastolic LV sphericity indices, consistent with a more normative change in LV cavity shape. As discussed below, CRT-mediated reductions of mitral regurgitation might also promote reverse modelling. The effect on reverse remodelling of other experimental therapies for heart failure, such as neuromodulation (the broad class of therapies include baroreceptor, vagal, and spinal-cord stimulation and cardiac contractility modulation), has not been studied; nor have the effects of neprilysin inhibition. The latest data on reverse remodelling is on the effects of mitral valve therapies and LVAD support.

Mitral valve repair and replacement. A common consequence of ventricular remodelling in chronic heart failure is functional mitral regurgitation. As the failing ventricle dilates, apical and lateral papillary muscles are displaced, pulling the mitral valve leaflets downward and apart in a manner that prohibits proper coaptation[55]. At the same time, the presence of functional mitral regurgitation independently contributes to additional ventricular remodelling owing to the added volume load and to associated adverse clinical outcomes[56]. Therefore, reducing functional mitral regurgitation in heart failure would interrupt this positive feedback loop of progressive remodelling and worsening functional mitral regurgitation. In a single-centre, treatment-only study published in 2016, patients with severe functional mitral regurgitation treated with edge-to-edge mitral valve repair had average reductions of LV end-diastolic volume of 6 ml/m^2 at 1 month and 15 ml/m^2 at 6 months[57]. This reduction was associated with an average 35–42% improvement of ejection fraction and restoration of ventricular geometry to a more normal elliptical shape. By contrast, a prospective, randomized study to compare surgical mitral valve repair with mitral valve replacement in patients with severe ischaemic mitral regurgitation, mainly in the setting of combined CABG surgery, showed that LV end-systolic volume decreased similarly in both groups, by only ~6.6 ml/m^2 after 1 year of follow-up, with no significant change in LVEF[58]. Similar findings (that is, no further improvement) were reported at 2 years of follow-up[59]. Therefore, both surgical repair and replacement resulted in a similar small degree of reverse remodelling. Importantly, despite a markedly higher rate of recurrence of moderate-to-severe mitral regurgitation after repair compared with replacement (58.8% versus 3.8%; P <0.001), mortality was similar in both groups, although the incidence of heart failure exacerbations was lower in the replacement group[59].

To date, however, no randomized studies with a medically-managed comparator group are available to prove definitively the benefits of treating mitral regurgitation in patients with functional mitral regurgitation and heart failure with reduced LVEF. One ongoing study, the COAPT trial[60], is designed to compare clinical effects of percutaneous edge-to-edge repair versus medical therapy on clinical end points and ventricular reverse remodelling. As percutaneous therapies for functional mitral regurgitation advance, with reduction in the risk of procedural complications and improved effectiveness, the benefits of treating functional mitral regurgitation will be further clarified, including addressing the question of optimal timing of intervention[61,62].

LVAD support. As detailed above, the use of LVADs has been invaluable for the identification of mechanisms underlying reverse remodelling, not only because the use of LVADs allows myocardial tissue samples to be obtained, but more importantly, because LVADs are unique as a therapy: unlike all other therapies for heart failure, LVADs simultaneously provide profound mechanical unloading of the left ventricle, while improving systemic blood pressure and cardiac output, with secondary improvements in neurohormonal status. A few additional points on LVAD-induced reverse remodelling are worth noting. First, reverse remodelling with LVADs is dose-dependent, that is, LVADs that provide full circulatory support and a large degree of ventricular unloading result in a greater degree of LV size normalization than LVADs that provide partial support and lesser degrees of unloading[63]. Second, as noted above, administration of pharmacotherapy while receiving LVAD support can enhance the degree of reverse remodelling (FIG. 3c). However, the optimal

LV sphericity indices
The ratio of left ventricular (LV) long-axis length divided by LV short-axis length, during both systole and diastole.

Functional mitral regurgitation
Mitral regurgitation occurring as a result of ventricular remodelling when apical and lateral papillary muscle displacement pulls the leaflets downward and apart in a manner that prohibits proper coaptation; the valve leaflets are generally normal.

Mitral valve repair
A surgical or percutaneous procedure in which the mitral leaflets, annulus, and/or choardae tendinae are modified to improve leaflet coaptation and reduce the degree of mitral regurgitation.

Mitral valve replacement
A surgical procedure involving the replacement of the natural mitral valve with a mechanical or bioprosthetic mitral valve; percutaneous procedures are currently under development.

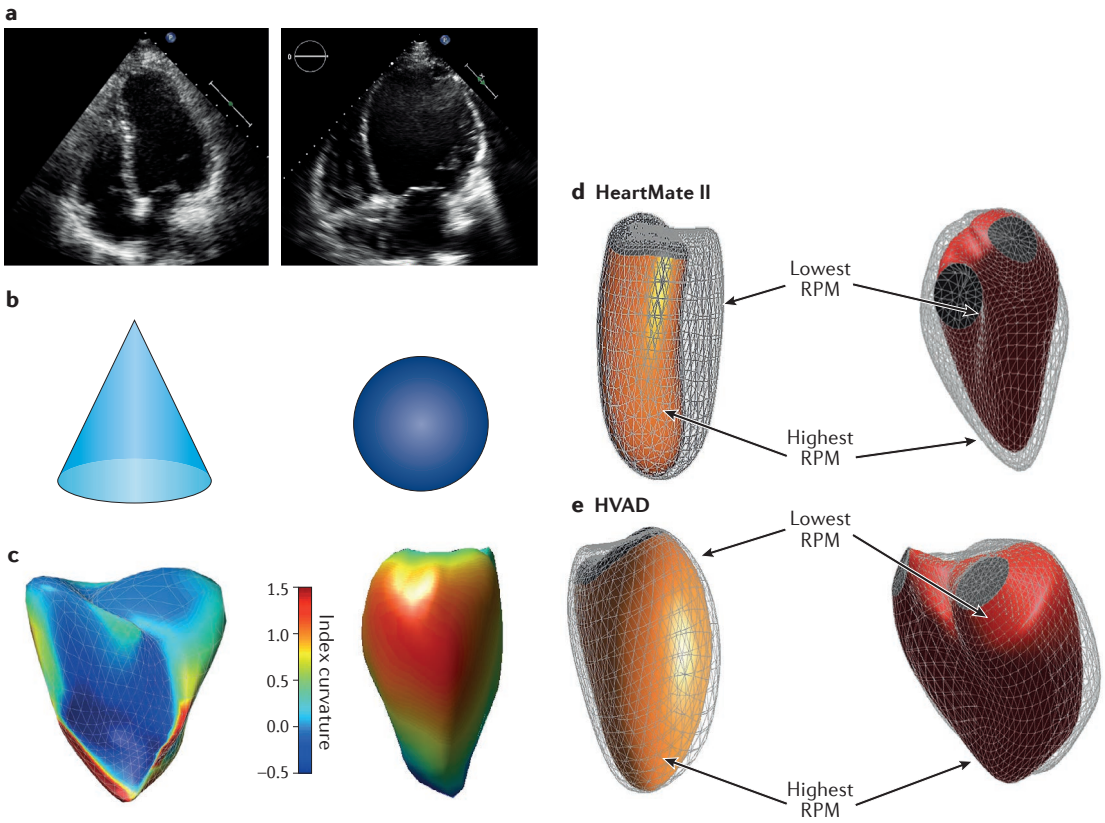


Figure 4 | **Metrics for echocardiographic assessment of myocardial recovery. a** | Left ventricular sphericity index based on 2D imaging with the use of maximal left ventricular long-axis internal dimension divided by the maximal short-axis internal dimension at end-diastole in a patient with a nonfailing heart (left panel) and a patient with dilated cardiomyopathy (right panel). **b** | Representative 3D-shape reference, either a sphere or a cone, to compare 3D reconstructed images of the left ventricle. **c** | Representative 3D endocardial surface analysis of the right ventricle (RV; left panel) and left ventricle (LV; right panel). **d,e** | Representative 3D endocardial surfaces of the LV (orange) and RV (red) obtained at the lowest and highest revolutions per minute (RPM), with HeartMate II (St. Jude Medical, USA; **d**) and HVAD (HeartWave, USA; **e**) left ventricular assist devices[69]. Surfaces obtained at lowest RPM, shown by the grey frame for the LV and the red frame for the RV, and the highest RPM, shown by the orange frame for the LV and by the grey frame for the RV, are superimposed in each panel. Figure adapted from Addetia, K. *et al.* 3D morphological changes in LV and RV during LVAD ramp studies. *JACC Cardiovasc. Imaging* http://dx.doi.org/10.1016/j.jcmg.2016.12.019 (2017), with permission from Elsevier.

combination of agents required to enhance reverse remodelling and, perhaps more importantly, achieve myocardial recovery to the point of enabling explantation of the LVAD is currently unknown. Early studies showed that use of aggressive neurohormonal blockade in addition to the β-agonist clembuterol promoted successful recovery of ventricular function to the point of device explantation[63,64]. Since the publication of these results, however, the reported range of myocardial recovery with the combination of LVAD support and medical therapy leading to device explantation remains highly variable[65]. In a study published in 2016, analysis of data from the Utah Cardiac Recovery Program did show that use of β-blockers, ACE inhibitors, angiotensin-receptor blockers, or mineralocorticoid-receptor antagonists was more frequent among patients with LVAD support who could have the device explanted owing to improved myocardial function[66]. Additional reports of relapse of heart failure following LVAD explantation, combined with the molecular findings noted above showing that many myocardial abnormalities persist after reverse remodelling, has led to the concept that, at best, the reverse-remodelled left ventricle that demonstrates improved (or even normal) function is in 'remission' from heart failure, rather than truly recovered[11].

New insights from echocardiography

The initial clinical studies of reverse remodelling focused on high-level structural and functional aspects, such as leftward shift of the EDPVR towards normal values and reductions in LV dimension, volume, wall thicknesses, and mass. Newer echocardiographic parameters have emerged since those early studies that have been used to characterize reverse remodelling after device and medical therapies (FIG. 4). Measurements such as LV shape[67], 2D strain imaging, torsion, and 3D echocardiographic assessments of LV and RV volumes and geometries have been explored[68]. Two interesting and relevant findings have emerged from such studies[69]. First, different LVADs have different effects on geometrical reverse remodelling: intrathoracic devices tend to push the LV apex towards the base, resulting in a more spherically

reverse-remodelled heart (FIG. 4d), whereas extrathoracic (pre-abdominal) devices pull the LV apex away from the base, resulting in a more elliptically reverse-remodelled heart (FIG. 4e). Whether these findings have any functional consequences is unknown. At least from reported registry experience, the rate of myocardial recovery or device explantation is similar with these two types of devices.

Second, findings from studies of changes of RV size and geometry, with special focus on changes in the position and curvature of the interventricular septum, will be important (FIG. 4c). Such studies, still in their infancy, aim to understand the role of changes in the neurohormonal milieu and loading conditions in the changes in RV function (including the role of interventricular interactions[13,14,70]) during LVAD support. Of note, in contrast to the left ventricle, the volume load on the right ventricle can increase during LVAD support, and the right ventricle does not reach the same degree of reverse remodelling as the left ventricle (FIG. 4d,e). Right heart failure is an important clinical problem both in the short term and the long term, and is the cause of a large proportion of repeat hospitalizations after LVAD implantation[71,72]. Whether this dysfunction has any additional implications in the persistent limitation in exercise tolerance seen in patients with reverse remodelling or in the overall rate of recovery from heart failure are important unanswered questions.

Implications of reverse remodelling

Exercise tolerance. One of the challenges in the study of reverse remodelling is the link between improved LV structure and function and improvements in a patient's exercise tolerance. Exercise tolerance remains limited with LVAD therapy, despite demonstration of significant ventricular reverse remodelling[73,74]. As exercise tolerance is probably linked directly with peak oxygen delivery, the low exercise tolerance in these patients might largely be attributed to the upper limit on blood-flow pumping of the LVAD. However, one study including 30 patients with a HeartMate II (St. Jude Medical, USA) LVAD who underwent exercise bicycle testing to evaluate exercise and pump performance after LVAD implantation showed that approximately half of the total cardiac output during exercise was derived from the native left ventricle and half was derived from the LVAD[75]. This finding demonstrates that in patients with LVADs who have substantially reverse-remodelled hearts, restoration of native LV contractility can provide additional blood flow to the flow provided by the LVAD. Therefore, additional metrics for reverse remodelling in patients with LVADs, including RV remodelling, might better predict improvement in functional capacity. Understanding and improving exercise tolerance in patients with LVADs and the link to reverse remodelling is a high-priority topic as more patients are implanted for destination therapy who are expected to be on support for many years.

CRT is also associated with improved exercise tolerance, and this improvement might, at least in part, be linked with reverse remodelling. Patients with CRT who have a LV end-systolic volume decrease of ≥15% had a higher peak oxygen consumption and better exercise performance than those who did not have an improvement in LV end-systolic volume at 6 months of follow-up[76]. Whereas some medical therapies induce reverse remodelling, as described above, these therapies are not uniformly associated with improved exercise tolerance in clinical studies[77]. This observation suggests that any mechanistic link between reverse remodelling and reduced mortality is independent of the effects of reverse remodelling on exercise tolerance.

Clinical outcomes. The 2013 ACC/AHA guidelines on heart failure management include a new classification of heart failure with preserved ejection fraction for those patients who have demonstrated reverse remodelling (defined as heart failure with improved ejection fraction), and indicate that these patients might be distinct from those with preserved or reduced ventricular function[78]. This new diagnostic entity primarily includes patients who have demonstrated marked improvements in LVEF in response to drug therapy and CRT. Long-term outcomes of patients who have reverse remodelling are still being assessed, but initial reports suggest that patients who achieve reverse remodelling with heart failure therapies have a better prognosis than those patients who do not[79,80]. However, another study showed that even after 8 years of normalized LV function, >30% of the patients experienced deterioration of LV systolic function and 5% died or underwent heart transplantation, underscoring the difference between myocardial remission[11] and recovery[79].

Data from multiple studies have further supported the notion that heart failure with recovered ejection fraction is a distinct clinical entity, whether shown by abnormal biochemical parameters suggesting some persistent degree of neurohormonal activation or by recurrence of substantial heart failure symptoms and clinical events such as cardiac hospitalizations[81,82] (TABLE 2). The implication is that neurohormonal blockade remains important and, therefore, the consensus recommendation in the setting of the reverse-remodelled heart is to continue therapy with ACE inhibitors or angiotensin-receptor blockers and β-blockers[83].

Mechanical unloading of the heart can consistently lead to the greatest degree of reverse remodelling observed with any known therapy, and can partially normalize the derangements seen at the cellular level. However, the incidence of myocardial recovery is low based on the data from the United Network of Organ Sharing (UNOS), which indicates a 1.4% rate of LVAD explantation owing to myocardial recovery[84]. Nevertheless, reported rates of LVAD explantation owing to cardiac recovery are highly variable depending on heart failure pathogenesis, weaning criteria, and protocols used, ranging from 4.5% to 45.0%[65]. This wide range might reflect differences in patient selection, with a varying probability of showing improved LV function during LVAD support[11,85]. Indeed, lack of uniformity in the assessment of reverse remodelling or in the protocol used to assess recovery also confounds any estimation of the incidence of reverse remodelling or remission[65,86].

Table 2 | **Clinical outcomes in patients with recovered or improved ejection fraction**

Study	Design	Results	Conclusion	Refs
Punnoose *et al.* (2011)	• Retrospective, chart-review, cross-sectional analysis • 121 patients with heart failure with recovered EF • Compared patients with EF >40%, and patients with EF <40%	• Similar characteristics in the recovered EF and low EF groups compared with the preserved EF group, but patients with recovered EF were younger, had less ischaemic disease, and were less symptomatic • The recovered EF group had larger LVEDD than the preserved EF group (5.1 cm versus 4.6 cm)	Individuals with recovered EF are clinically distinct	80
Basuray *et al.* (2014)	• Prospective cohort study (2003–2012) • 1,821 patients with heart failure in total • 176 patients with recovered EF	• Recovered EF group had improved survival compared with patients with reduced or preserved EF • Recovered EF group had a risk of cardiac hospitalization similar to the preserved EF cohort • Recovered EF group had abnormal levels of BNP, uric acid, protein ST2, and VEGFR1	The patient population with recovered EF represents a distinct heart failure phenotype, with biochemical parameters suggesting persistent pathology	82
De Groote *et al.* (2014)	• 174 consecutive patients (1998–2004) with recovered EF ≥45% • Median follow-up 9.2 (7.2–10.8) years • Patients were receiving angiotensin-converting enzyme inhibitor therapy, then started on a β-blocker	• EF deteriorated in 25% of study population after 8 years of follow-up	Despite reverse remodelling, EF decreased, with an increase in cardiovascular mortality	81
Merlo *et al.* (2015)	• Observational, retrospective study • 408 patients with dilated cardiomyopathy with long-term follow-up (>100 months), EF >50%, and normal LVID • Patients treated with optimal medical therapy	• 37% of this subgroup experienced deterioration of left ventricular systolic function	Patients who have a recovered EF even in the long term cannot be considered effectively healed, and should be carefully treated and monitored	79

BNP, B-type natriuretic peptide; EF, ejection fraction; LVEDD, left ventricular end-diastolic dimension; LVID, left ventricular internal diameter; VEGFR1, vascular endothelial growth factor receptor 1.

Ultimately, why reverse remodelling is sometimes associated with myocardial recovery and why heart failure events can recur despite reverse modelling is unclear. Reported relapses of heart failure after explantation of LVAD support have given rise to the term remission to describe the normalization of certain molecular changes and global ventricular geometry, which can indeed be associated with stabilization of the clinical course of heart failure. However, remission is not necessarily associated with freedom from future cardiac events and, therefore, is considered to be distinct from myocardial recovery.

Does aetiology affect reverse remodelling and recovery?

LV remodelling and dysfunction are the common phenotypic manifestations of a diverse range of insults, either systemic or heart-specific. A necessary complexity to the translational investigation of human heart failure is the acceptance of multifactorial inputs into the failing myocardium. Myocardial recovery (or remission) can occur, but is more likely to be seen in nonischaemic cardiomyopathies, younger patients, and patients with a more recent onset of the disease. These characteristics overlap with those of patients who are more likely to recover with other forms of therapy, including β-blockers and CRT[66]. To understand the effect of aetiology, differentiating reverse remodelling from recovery is important. Patients with ischaemic cardiomyopathy and patients with dilated (nonischaemic) cardiomyopathy have, on average, the same degree of reverse structural remodelling, normalization of genes related to calcium cycling, and recovery of myocardial responsiveness to β-adrenergic stimulation. However, fundamental issues arise when assessing the potential for 'recovery' in these patients. First, the underlying cause of ischaemic cardiomyopathy is loss of myocardial muscle mass owing to previous infarction, with or without ongoing ischaemia as a result of residual coronary artery disease. In the chronic setting, the remaining viable myocardium undergoes characteristic (partially irreversible) changes owing to the long-term exposure to mechanical and biochemical stresses. However, even if the heart structure and viable myocardium could be reverse remodelled all the way back to normal, the heart would still probably be weak owing to the loss of myocardial muscle mass, which is not replaced by any currently available therapy.

Secondly, nonischaemic dilated cardiomyopathies are a heterogeneous group of molecular diseases. A study to assess the normalization of LV function in varied clinical settings in patients with recent-onset dilated cardiomyopathy showed that patients with underlying aetiologies such as stress-induced, hyperthyroidism-induced, and tachycardia-induced cardiomyopathies had a higher degree of LV function recovery than those with aetiologies related to toxins or inflammatory states[85]. Beyond these aetiologies, dilated cardiomyopathy remains strongly related to genetic susceptibility, although this susceptibility is often not identified with genetic testing. For example, truncating variants in the gene encoding titin (*TTN*) can be found in 25% of patients with familial dilated cardiomyopathy and in 18% of patients with sporadic dilated cardiomyopathy[87]. However, dilated cardiomyopathies associated with *TTN*-truncating mutations are more amenable to standard afterload

reduction and neurohumoral blockade therapies than those with other mutations[88]. Interestingly, a study showed that six out of ten patients with a *TTN*-truncating variant recovered sufficient cardiac function to enable LVAD explantation[89], underscoring the possibility of reverse remodelling with some genetic forms of dilated cardiomyopathy and also highlighting the importance of defining genetic aetiology. A study to evaluate the UNOS registry data on patients supported with HeartMate II and HVAD (HeartWare, USA) LVADs showed that 5% of these patients had the LVAD explanted owing to recovered LV function[84]. Of the patients with recovered LV function, 91% had non-ischaemic aetiology, compared with 59% in the group that ultimately required heart transplantation[84].

Conclusions

Interest in the phenomena surrounding myocardial reverse remodelling and recovery has increased with current therapies for heart failure including neurohormonal blockade and device therapies such as CRT and LVADs. Despite normalization of ventricular chamber dimension and LV function with these therapeutic strategies, most recent data show that major abnormalities at the molecular level persist. New genotypes appear in the reverse-remodelled myocardium, the functional consequences of which are unknown. Consistent with these new molecular insights, reports show that patients with phenotypic remission of heart failure continue to be at risk of cardiovascular events, and therefore should be treated with optimal heart failure therapies.

Accumulating evidence shows that reverse remodelling and recovery are not synonymous, neither at the cellular level nor at the ventricular level. However, all results indicate that the earlier the disease process is interrupted, the greater is the likelihood of remission and more complete return to normal heart function. Therefore, the current clinical challenge is the early identification of the heart failure state and the most appropriate intervention. Additionally, current studies highlighted in this Review indicate the incomplete nature of cellular normalization in myocardial reverse remodelling; these findings emphasize the need to continue discovering the modifiable factors, such as transcriptomic and metabolic factors, that influence the path from myocardial reverse remodelling to recovery.

1. Hochman, J. S. & Bulkley, B. H. Expansion of acute myocardial infarction: an experimental study. *Circulation* **65**, 1446–1450 (1982).
2. Erlebacher, J. A. *et al.* Late effects of acute infarct dilation on heart size: a two dimensional echocardiographic study. *Am. J. Cardiol.* **49**, 1120–1126 (1982).
3. Pfeffer, J. M., Pfeffer, M. A., Fletcher, P. J. & Braunwald, E. Progressive ventricular remodeling in rat with myocardial infarction. *Am. J. Physiol.* **260**, H1406–H1414 (1991).
4. Burkhoff, D. *et al.* In vitro studies of isolated supported human hearts. *Heart Vessels* **4**, 185–196 (1988).
5. Cohn, J. N., Ferrari, R. & Sharpe, N. Cardiac remodeling — concepts and clinical implications: a consensus paper from an International Forum on Cardiac Remodeling. *J. Am. Coll. Cardiol.* **35**, 569–582 (2000).
6. Saraon, T. & Katz, S. D. Reverse remodeling in systolic heart failure. *Cardiol. Rev.* **23**, 173–181 (2015).
7. Levin, H. R. *et al.* Reversal of chronic ventricular dilation in patients with end-stage cardiomyopathy by prolonged mechanical unloading. *Circulation* **91**, 2717–2720 (1995).
8. Burkhoff, D., Klotz, S. & Mancini, D. M. LVAD-induced reverse remodeling: basic and clinical implications for myocardial recovery. *J. Card. Fail.* **12**, 227–239 (2006).
9. Hall, J. L. *et al.* Clinical, molecular, and genomic changes in response to a left ventricular assist device. *J. Am. Coll. Cardiol.* **57**, 641–652 (2011).
10. Uriel, N., Kim, G. H. & Burkhoff, D. Myocardial recovery after LVAD implantation: a vision or simply an illusion? *J. Am. Coll. Cardiol.* **70,** 355–357 (2017).
11. Mann, D. L., Barger, P. M. & Burkhoff, D. Myocardial recovery and the failing heart: myth, magic, or molecular target? *J. Am. Coll. Cardiol.* **60**, 2465–2472 (2012).
12. Madigan, J. D. *et al.* Time course of reverse remodeling of the left ventricle during support with a left ventricular assist device. *J. Thorac. Cardiovasc. Surg.* **121**, 902–908 (2001).
13. Barbone, A. *et al.* Comparison of right and left ventricular responses to left ventricular assist device support in patients with severe heart failure: a primary role of mechanical unloading underlying reverse remodeling. *Circulation* **104**, 670–675 (2001).
14. Klotz, S. *et al.* Left ventricular assist device support normalizes left and right ventricular beta-adrenergic pathway properties. *J. Am. Coll. Cardiol.* **45**, 668–676 (2005).
15. Rajabi, M., Kassiotis, C., Razeghi, P. & Taegtmeyer, H. Return to the fetal gene program protects the stressed heart: a strong hypothesis. *Heart Fail. Rev.* **12**, 331–343 (2007).
16. Margulies, K. B. *et al.* Mixed messages: transcription patterns in failing and recovering human myocardium. *Circ. Res.* **96**, 592–599 (2005).
17. Hall, J. L. *et al.* Genomic profiling of the human heart before and after mechanical support with a ventricular assist device reveals alterations in vascular signaling networks. *Physiol. Genomics* **17**, 283–291 (2004).
18. Birks, E. J. *et al.* Gene profiling changes in cytoskeletal proteins during clinical recovery after left ventricular-assist device support. *Circulation* **112**, I57–I64 (2005).
19. Ton, V. K., Vunjak-Novakovic, G. & Topkara, V. K. Transcriptional patterns of reverse remodeling with left ventricular assist devices: a consistent signature. *Expert Rev. Med. Devices* **13**, 1029–1034 (2016).
20. Epelman, S., Liu, P. P. & Mann, D. L. Role of innate and adaptive immune mechanisms in cardiac injury and repair. *Nat. Rev. Immunol.* **15**, 117–129 (2015).
21. Topkara, V. K. *et al.* Functional significance of the discordance between transcriptional profile and left ventricular structure/function during reverse remodeling. *JCI Insight* **1**, e86038 (2016).
22. Movassagh, M. *et al.* Distinct epigenomic features in end-stage failing human hearts. *Circulation* **124**, 2411–2422 (2011).
23. Matkovich, S. J. *et al.* Reciprocal regulation of myocardial microRNAs and messenger RNA in human cardiomyopathy and reversal of the microRNA signature by biomechanical support. *Circulation* **119**, 1263–1271 (2009).
24. Heerdt, P. M. *et al.* Chronic unloading by left ventricular assist device reverses contractile dysfunction and alters gene expression in end-stage heart failure. *Circulation* **102**, 2713–2719 (2000).
25. Yang, K. C. *et al.* Deep RNA sequencing reveals dynamic regulation of myocardial noncoding RNAs in failing human heart and remodeling with mechanical circulatory support. *Circulation* **129**, 1009–1021 (2014).
26. Ramani, R. *et al.* A micro-ribonucleic acid signature associated with recovery from assist device support in 2 groups of patients with severe heart failure. *J. Am. Coll. Cardiol.* **58**, 2270–2278 (2011).
27. Akat, K. M. *et al.* Comparative RNA-sequencing analysis of myocardial and circulating small RNAs in human heart failure and their utility as biomarkers. *Proc. Natl Acad. Sci. USA* **111**, 11151–11156 (2014).
28. Bär, C., Chatterjee, S. & Thum, T. Long noncoding RNAs in cardiovascular pathology, diagnosis, and therapy. *Circulation* **134**, 1484–1499 (2016).
29. Kumarswamy, R. *et al.* Circulating long non-coding RNA, LIPCAR, predicts survival in patients with heart failure. *Circ. Res.* **114**, 1569–1575 (2014).
30. Lee, J. H. *et al.* Analysis of transcriptome complexity through RNA sequencing in normal and failing murine hearts. *Circ. Res.* **109**, 1332–1341 (2011).
31. Viereck, J. & Thum, T. Long noncoding RNAs in pathological cardiac remodeling. *Circ. Res.* **120**, 262–264 (2017).
32. Ashrafian, H., Frenneaux, M. P. & Opie, L. H. Metabolic mechanisms in heart failure. *Circulation* **116**, 434–448 (2007).
33. Wallhaus, T. R. *et al.* Myocardial free fatty acid and glucose use after carvedilol treatment in patients with congestive heart failure. *Circulation* **103**, 2441–2446 (2001).
34. Kodde, I. F., van der Stok, J., Smolenski, R. T. & de Jong, J. W. Metabolic and genetic regulation of cardiac energy substrate preference. *Comp. Biochem. Physiol. A Mol. Integr. Physiol.* **146**, 26–39 (2007).
35. Aubert, G. *et al.* The failing heart relies on ketone bodies as a fuel. *Circulation* **133**, 698–705 (2016).
36. Bedi, K. C. Jr *et al.* Evidence for intramyocardial disruption of lipid metabolism and increased myocardial ketone utilization in advanced human heart failure. *Circulation* **133**, 706–716 (2016).
37. Diakos, N. A. *et al.* Evidence of glycolysis up-regulation and pyruvate mitochondrial oxidation mismatch during mechanical unloading of the failing human heart: implications for cardiac reloading and conditioning. *JACC Basic Transl. Sci.* **1**, 432–444 (2016).
38. Spinale, F. G. Myocardial matrix remodeling and the matrix metalloproteinases: influence on cardiac form and function. *Physiol. Rev.* **87**, 1285–1342 (2007).
39. Borg, T. K. & Caulfield, J. B. The collagen matrix of the heart. *Fed. Proc.* **40**, 2037–2041 (1981).
40. Takawale, A., Sakamuri, S. S. & Kassiri, Z. Extracellular matrix communication and turnover in cardiac physiology and pathology. *Compr. Physiol.* **5**, 687–719 (2015).
41. Klotz, S. *et al.* The impact of angiotensin-converting enzyme inhibitor therapy on the extracellular collagen matrix during left ventricular assist device support in patients with end-stage heart failure. *J. Am. Coll. Cardiol.* **49**, 1166–1174 (2007).
42. Spinale, F. G. *et al.* A matrix metalloproteinase induction/activation system exists in the human left ventricular myocardium and is upregulated in heart failure. *Circulation* **102**, 1944–1949 (2000).
43. Klotz, S. *et al.* Mechanical unloading during left ventricular assist device support increases left ventricular collagen cross-linking and myocardial stiffness. *Circulation* **112**, 364–374 (2005).

44. Sakamuri, S. S. *et al.* Differential impact of mechanical unloading on structural and nonstructural components of the extracellular matrix in advanced human heart failure. *Transl. Res.* **172**, 30–44 (2016).
45. Valiente-Alandi, I., Schafer, A. E. & Blaxall, B. C. Extracellular matrix-mediated cellular communication in the heart. *J. Mol. Cell. Cardiol.* **91**, 228–237 (2016).
46. Rienks, M. & Papageorgiou, A. P. Novel regulators of cardiac inflammation: matricellular proteins expand their repertoire. *J. Mol. Cell. Cardiol.* **91**, 172–178 (2016).
47. Pfeffer, M. A. Mechanistic lessons from the SAVE Study. *Am. J. Hypertens.* **7**, 106S–111S (1994).
48. Zannad, F. *et al.* Mineralocorticoid receptor antagonists for heart failure with reduced ejection fraction: integrating evidence into clinical practice. *Eur. Heart J.* **33**, 2782–2795 (2012).
49. Groenning, B. A. *et al.* Antiremodeling effects on the left ventricle during beta-blockade with metoprolol in the treatment of chronic heart failure. *J. Am. Coll. Cardiol.* **36**, 2072–2080 (2000).
50. Hall, S. A. *et al.* Time course of improvement in left ventricular function, mass and geometry in patients with congestive heart failure treated with beta-adrenergic blockade. *J. Am. Coll. Cardiol.* **25**, 1154–1161 (1995).
51. Bristow, M. R. *et al.* Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N. Engl. J. Med.* **350**, 2140–2150 (2004).
52. Cleland, J. G. *et al.* The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N. Engl. J. Med.* **352**, 1539–1549 (2005).
53. Yu, C. M. *et al.* Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. *Circulation* **105**, 438–445 (2002).
54. Sutton, M. G. *et al.* Sustained reverse left ventricular structural remodeling with cardiac resynchronization at one year is a function of etiology: quantitative Doppler echocardiographic evidence from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE). *Circulation* **113**, 266–272 (2006).
55. Enriquez-Sarano, M., Akins, C. W. & Vahanian, A. Mitral regurgitation. *Lancet* **373**, 1382–1394 (2009).
56. Cleland, J. *et al.* Predicting the long-term effects of cardiac resynchronization therapy on mortality from baseline variables and the early response a report from the CARE-HF (Cardiac Resynchronization in Heart Failure) Trial. *J. Am. Coll. Cardiol.* **52**, 438–445 (2008).
57. Gripari, P. *et al.* Three-dimensional transthoracic echocardiography in the comprehensive evaluation of right and left heart chamber remodeling following percutaneous mitral valve repair. *J. Am. Soc. Echocardiogr.* **29**, 946–954 (2016).
58. Acker, M. A. *et al.* Mitral-valve repair versus replacement for severe ischemic mitral regurgitation. *N. Engl. J. Med.* **370**, 23–32 (2014).
59. Goldstein, D. *et al.* Two-year outcomes of surgical treatment of severe ischemic mitral regurgitation. *N. Engl. J. Med.* **374**, 344–353 (2016).
60. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT01626079?term = NCT01626079 (2017).
61. Burkhoff, D. & Guccione, J. A new twist on mitral regurgitation. *JACC Basic Transl. Sci.* **1**, 203–206 (2016).
62. Notomi, Y. *et al.* Pre-operative left ventricular torsion, QRS width/CRT, and post-mitral surgery outcomes in patients with nonischemic, chronic, severe secondary mitral regurgitation. *JACC Basic Transl. Sci.* **1**, 193–202 (2016).
63. Birks, E. J. *et al.* Reversal of severe heart failure with a continuous-flow left ventricular assist device and pharmacological therapy: a prospective study. *Circulation* **123**, 381–390 (2011).
64. Birks, E. J. *et al.* Left ventricular assist device and drug therapy for the reversal of heart failure. *N. Engl. J. Med.* **355**, 1873–1884 (2006).
65. Drakos, S. G. & Mehra, M. R. Clinical myocardial recovery during long-term mechanical support in advanced heart failure: insights into moving the field forward. *J. Heart Lung Transplant.* **35**, 413–420 (2016).
66. Wever-Pinzon, O. *et al.* Cardiac recovery during long-term left ventricular assist device support. *J. Am. Coll. Cardiol.* **68**, 1540–1553 (2016).
67. Waring, A. A. & Litwin, S. E. Redefining reverse remodeling: can echocardiography refine our ability to assess response to heart failure treatments? *J. Am. Coll. Cardiol.* **68**, 1277–1280 (2016).
68. Kapetanakis, S. *et al.* Real-time 3D echo in patient selection for cardiac resynchronization therapy. *JACC Cardiovasc. Imaging* **4**, 16–26 (2011).
69. Addetia, K. *et al.* 3D morphological changes in LV and RV during LVAD ramp studies. *JACC Cardiovasc. Imaging* http://dx.doi.org/10.1016/j.jcmg.2016.12.019 (2017).
70. Woodard, J. C. *et al.* Computer model of ventricular interaction during left ventricular circulatory support. *ASAIO Trans.* **35**, 439–441 (1989).
71. Mehra, M. R. *et al.* A fully magnetically levitated circulatory pump for advanced heart failure. *N. Engl. J. Med.* **376**, 440–450 (2016).
72. Lampert, B. C. & Teuteberg, J. J. Right ventricular failure after left ventricular assist devices. *J. Heart Lung Transplant.* **34**, 1123–1130 (2015).
73. de Jonge, N. *et al.* Exercise performance in patients with end-stage heart failure after implantation of a left ventricular assist device and after heart transplantation: an outlook for permanent assisting? *J. Am. Coll. Cardiol.* **37**, 1794–1799 (2001).
74. Jaski, B. E. *et al.* Comparison of functional capacity in patients with end-stage heart failure following implantation of a left ventricular assist device versus heart transplantation: results of the experience with left ventricular assist device with exercise trial. *J. Heart Lung Transplant.* **18**, 1031–1040 (1999).
75. Martina, J. *et al.* Exercise hemodynamics during extended continuous flow left ventricular assist device support: the response of systemic cardiovascular parameters and pump performance. *Artif. Organs* **37**, 754–762 (2013).
76. Mastenbroek, M. H. *et al.* Relationship between reverse remodeling and cardiopulmonary exercise capacity in heart failure patients undergoing cardiac resynchronization therapy. *J. Card. Fail.* **22**, 385–394 (2016).
77. Metra, M. *et al.* Effects of neurohormonal antagonism on symptoms and quality-of-life in heart failure. *Eur. Heart J.* **19** (Suppl. B), B25–B35 (1998).
78. Yancy, C. W. *et al.* 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* **128**, 1810–1852 (2013).
79. Merlo, M. *et al.* Persistent recovery of normal left ventricular function and dimension in idiopathic dilated cardiomyopathy during long-term follow-up: does real healing exist? *J. Am. Heart Assoc.* **4**, e001504 (2015).
80. Punnoose, L. R. *et al.* Heart failure with recovered ejection fraction: a distinct clinical entity. *J. Card. Fail.* **17**, 527–532 (2011).
81. de Groote, P. *et al.* Long-term functional and clinical follow-up of patients with heart failure with recovered left ventricular ejection fraction after beta-blocker therapy. *Circ. Heart Fail.* **7**, 434–439 (2014).
82. Basuray, A. *et al.* Heart failure with recovered ejection fraction: clinical description, biomarkers, and outcomes. *Circulation* **129**, 2380–2387 (2014).
83. Stevenson, L. W. Heart failure with better ejection fraction: a modern diagnosis. *Circulation* **129**, 2364–2367 (2014).
84. Pan, S. *et al.* Incidence and predictors of myocardial recovery on long-term left ventricular assist device support: results from the United Network for Organ Sharing database. *J. Heart Lung Transplant.* **34**, 1624–1629 (2015).
85. Givertz, M. M. & Mann, D. L. Epidemiology and natural history of recovery of left ventricular function in recent onset dilated cardiomyopathies. *Curr. Heart Fail. Rep.* **10**, 321–330 (2013).
86. Basuray, A. & Fang, J. C. Management of patients with recovered systolic function. *Prog. Cardiovasc. Dis.* **58**, 434–443 (2016).
87. Herman, D. S. *et al.* Truncations of titin causing dilated cardiomyopathy. *N. Engl. J. Med.* **366**, 619–628 (2012).
88. Jansweijer, J. A. *et al.* Truncating titin mutations are associated with a mild and treatable form of dilated cardiomyopathy. *Eur. J. Heart Fail.* **19**, 512–521 (2017).
89. Felkin, L. E. *et al.* Recovery of cardiac function in cardiomyopathy caused by titin truncation. *JAMA Cardiol.* **1**, 234–235 (2016).
90. Maybaum, S. *et al.* Cardiac improvement during mechanical circulatory support: a prospective multicenter study of the LVAD Working Group. *Circulation* **115**, 2497–2505 (2007).
91. Bruggink, A. H. *et al.* Reverse remodeling of the myocardial extracellular matrix after prolonged left ventricular assist device support follows a biphasic pattern. *J. Heart Lung Transplant.* **25**, 1091–1098 (2006).

Author contributions

All authors researched the data for the article, provided substantial contributions to discussions of its content, wrote the article, and undertook review and/or editing of the manuscript before submission.

Competing interests statement

N.U. has received grant support from HeartWare and Thoratec; and has served as a consultant for Abiomed, HeartWare (Medtronic), and Medtronic. D.B. is a consultant for BackBeat Medical, Cardiac Implants, HeartWare (Medtronic), Impulse Dynamics, and Sensible Medical. The Cardiovascular Research Foundation is the recipient of an unrestricted educational grant from Abiomed. G.H.K. declares no competing interests.

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.