Remodeling: What Has Changed Over the Past 10 Years?

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Some terms in cardiology attempt to encapsulate a highly complex concept by bestowing a single, striking, vivid, intriguing—but let us admit it—occasionally cryptic name. Typical examples are the often used “trio” of “stunning,” hibernation,” and “remodeling.”

Although these terms became instantly popular and etched in memory, they hardly “speak for themselves,” or, rather, they “speak volumes,” inasmuch as they give rise to very different interpretations depending on who is using them.

Thus, the perception of the term “cardiac remodeling” varies according to whether one is a cardiologist, assessing the effect of remodeling on the ventricle's pumping capacity; a pathologist, for whom remodeling means hypertrophy, fibrosis, or apoptosis; or a molecular biology, who considers remodeling in terms of upregulation or downregulation of various pathways and proteins in the myocyte or interstitium.

The term “cardiac remodeling” was coined by Janice Pfeffer in the mid-1980s to designate the prominent changes in cardiac structure that occur after myocardial infarction. It quickly became clear that these changes could have other causes, eg, hypertension, aortic valve stenosis, myocarditis, valvular regurgitation, etc, and that the changes themselves were more complex in type and scope than initially thought. Dialogues devoted an entire issue to “Cardiac Remodeling” in 1999 (Vol. 4[No. 1]), and Karl T. Weber et al, in their Lead article (pp 3-19) took stock of the diversity of meanings of the term “myocardial remodeling”:

“The term remodeling is used frequently and can have different meanings. It may indicate:
(i) architectural (or geometrical) iterations in ventricular size and shape and the thickness of its wall;
(ii) biochemical modifications of cardiac myocytes, such as myosin light chain phosphorylation, or expression of myocyte genes that favor iterations in myosin isoform composition or which induce programmed cell death (apoptosis); or (iii) structural alterations of infarcted tissue and viable myocardium remote to the site of MI by fibrous tissue.”
Over the past 10 years, the scene has greatly evolved. Accordingly, a fresh look at cardiac remodeling is long overdue.

The Lead article by John Cleland addresses both ventricular and atrial remodeling (the latter being a major substrate for atrial fibrillation), as well as the remodeling of the vasculature and its implications for hypertension. The concept of cardiac remodeling is also pivotal in explaining the effects of many classes of medicines, such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, ivabradine, etc. Not only can pharmacological interventions reshape the ventricle, but also devices such as cardiac resynchronization therapy. As always, the cardiologist sees only the tip of the iceberg, which is improved cardiac structure and function. Under the surface, enormous changes in the heart’s molecular structure must occur. If the molecular secrets of remodeling could be unlocked, this could lead to more specific interventions to induce cardiac repair and regeneration.

The three Expert Answer articles address specific issues of current interest. Beyond the well-known role of increased afterload in cardiac remodeling, Michel Komajda looks at the increasing understanding of the role of heart rate. This is of course very important to explain the positive effects of the β-blockers and ivabradine. Paola Rizzo and Pietro Ameri concentrate on the changes induced by cardiac remodeling at the molecular level that affect intracellular and intercellular signaling and the cardiac myocyte’s life-and-death cycle, in particular the role of the “Notch” signaling pathway. Lastly, Shahab Ghaefghazi, Marcin Wysoczynski, Matthew C. L. Keith, Joseph B. Moore, and Roberto Bolli discuss whether ventricular remodeling might supplant left ventricular ejection fraction (LVEF) as the surrogate end point of choice for cell-based therapy in clinical trials.
Cardiac remodeling: what has changed over the past 10 years?

John G. F. Cleland, MD, PhD, FRCP, FESC, FACC
Professor of Clinical Cardiology - Royal Brompton & Harefield Hospitals - Imperial College - London - UK

Cardiac remodeling, perhaps more precisely termed myocardial remodeling, will occur either in response to changes in loading conditions that may occur in health or disease or in response to diseases of the myocardium itself. Remodeling may be modified by trophic factors or the genetic substrate, and it may involve both death and proliferation of cardiac myocytes. The myocardium may be considered to be in a constant state of flux as it adapts to changing needs and the effects of the disease.

Conceptually, myocardial remodeling, both ventricular and atrial, is integral to heart failure development and recovery, and yet, there is a remarkable lack of robust information to support the translation of the theory that remodeling is a therapeutic target into clinical practice. Indeed, when remodeling has been targeted directly, it has often had adverse consequences. This article attempts to distinguish the clinical facts from concepts based on experimental models that may or may not be relevant from a clinical cardiologist’s or patient’s perspective. Other mechanisms by which heart failure may progress include worsening renal function, iron deficiency, anemia, pulmonary hypertension, and atrioventricular valve dysfunction, but these issues are beyond the scope of this article.

**SELECTED ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>ACE</td>
<td>angiotensin-converting enzyme</td>
</tr>
<tr>
<td>ARB</td>
<td>angiotensin receptor blocker</td>
</tr>
<tr>
<td>ARNI</td>
<td>angiotensin receptor blocker with a neprilysin inhibitor</td>
</tr>
<tr>
<td>CRT</td>
<td>cardiac resynchronization therapy</td>
</tr>
<tr>
<td>HFPEF</td>
<td>heart failure with preserved ejection fraction</td>
</tr>
<tr>
<td>HRF</td>
<td>heart failure with reduced ejection fraction</td>
</tr>
<tr>
<td>MRA</td>
<td>mineralocorticoid receptor antagonist</td>
</tr>
</tbody>
</table>

**Keywords:** heart failure; hypertension; hypertrophy; myocardial infarction; remodeling
DEFINITION OF CARDIAC OR MYOCARDIAL REMODELING

“It means just what I choose it to mean” from *Alice in Wonderland* (Lewis Carroll)

Cardiac remodeling is an evolving concept that has no precise definition (Figure 1).\(^8\,10\) Originally, the concept was applied almost exclusively to the left ventricle, but more recently, it has been applied to the right ventricle and the atria.\(^11\,14\) Remodeling places emphasis on structural changes, but structure and function are intimately related, therefore, abnormal function may also be considered remodeling. This must be distinguished from a normal physiological response to stress. The term “remodeling” is often used specifically to denote a response to hypertension, valve disease, or myocardial damage, and the term “reverse remodeling” to denote recovery. As we shall see, it is probably not appropriate to use the term “adverse remodeling.”

In clinical practice, remodeling is generally defined by changes in chamber volume or myocardial thickness or mass observed on cardiac imaging at rest. Improvements in imaging techniques have enabled investigation of the quality of the myocardium (scar, fibrosis, amyloid deposits, etc) and detection of subtle changes in function and performance before changes in structure occur, which might also be considered aspects of remodeling.\(^15\,16\) However, the growing evidence that plasma biomarkers are an even more sensitive and accurate measure of cardiac dysfunction is one of the most exciting developments in this field.\(^17\)

In experimental animal models, cardiac remodeling may also be assessed by imaging or biomarkers. In addition, remodeling can be assessed directly in tissues at the syncytial, cellular, subcellular, or molecular level.\(^8\) At a tissue level, remodeling may be described for cardiac myocyte size or shape, the volume and quality of the extracellular matrix, and the inflammatory response.\(^18\) At a subcellular level, changes in the disposition of sarcomeres, mitochondria, sarcoplasmic reticulum, transverse tubules, and mitochondria may all be observed during pathological remodeling.\(^19\) Remodeling can also take place at a molecular level and may be influenced by genetic factors.\(^20\,21\)

Animal models can provide insights into disease and potential therapeutic targets, but care should be taken to distinguish causal from casual associations. Studying the effects of genetic, pharmacological, or device-based interventions that perturb the system may help
identify pathways that have important mechanistic significance. Systems biology may also identify common “nodes” through which many key biological pathways travel, which are of fundamental importance to disease.22

Remodeling reflects a complex interplay between the demands placed on the heart and the health of the myocardium. Remodeling was “designed” to adapt the heart to the stress placed on it by the circulation. It is fundamentally a good thing and we interfere with it at our patient’s peril. All remodeling may be considered good, even if the reasons why it is necessary are often bad. Failing to remodel appropriately in the face of a large myocardial infarction, severe hypertension, or substantial valve disease may be lethal. So-called “reverse” remodeling, as the heart recovers from injury or in response to therapy, is a good prognostic sign. However, remodeling can be considered a barometer of health rather than a problem. Interventions designed to interfere directly with remodeling may be deleterious, whereas interventions that amplify some aspects of remodeling may be beneficial.23,24

**CLASSIFICATION OF REMODELING**

Clinically, remodeling is defined by chamber volume and wall thickness or mass, and is usually measured at rest. The heart is designed to receive blood at low pressure and deliver it at high pressure to the lungs and systemic circulation in the quantities required to maintain organ function and to do so both at rest and during exertion. The difficulty and complexity of measuring cardiac structure and function during exertion is an important limitation to the remodeling story. In health, cardiac chamber diastolic volumes will increase during blood volume expansion or exercise; this helps maintain a low filling pressure and increases cardiac output. Preload reserve is a sign of health, whereas the lack of preload reserve is a sign of congestion.25

**LEFT VENTRICULAR VOLUME**

Typically, left ventricular remodeling may be defined as a change in end-diastolic chamber volume, although some prefer end-systolic volume, which reflects both chamber dilatation and myocardial contraction.26 Pathological remodeling also involves a change in left ventricular shape from an efficient cone to a less efficient sphere (Figure 2).9,27 Shape changes may be rendered even more complex in patients with ischemic heart disease, who often have a large amount of scarred myocardium that may remodel in a different way and rate than the surviving myocardium.

There are huge conceptual problems about how to reliably measure left ventricular remodeling. Ideally, remodeling should be assessed using pressure-volume loops. Expansion or reduction in plasma volume due to the development of congestion and administration of diuretics will cause changes in chamber volumes, but clinical studies rarely control for this. Similarly, interventions that improve heart function may reduce cardiac volumes; however, if the effect disappears immediately after the intervention is stopped, this should not be considered remodeling. Heart rate is also im-
portant. In the short term, increases in heart rate will lead to a fall in left ventricular diastolic volume due to the shorter filling time, whereas pauses will lead to a larger end-diastolic volume and greater stroke volume in the following beat. Differences in ventricular volume should only be attributed to remodeling: (i) if they cannot be reasonably accounted for by changes in blood volume, loading pressures (diastolic and systolic), and heart rate, and (ii) after the intervention potentially involved in the remodeling has been stopped for several days. These conditions are rarely met in clinical practice.

As the ventricle dilates, even though myocardial compliance might be impaired, ventricular compliance increases and the ventricle can accommodate a larger volume without an increase in diastolic pressure. Increasing ventricular compliance further could be deleterious. Ventricular dilatation is also likely to provoke systolic mitral regurgitation. Delayed activation of the left ventricular free wall may also provoke dysynchrony and diastolic mitral regurgitation. Thus, although myocardial dysfunction is a trigger of left ventricular dysfunction, the two processes may often become dissociated.

**LEFT VENTRICULAR HYPTERTROPHY**

Left ventricular hypertrophy is an essential component of remodeling. In response to hypertension or aortic stenosis, concentric left ventricular hypertrophy occurs (Figure 1). In response to left ventricular dilatation, irrespective of cause, eccentric left ventricular hypertrophy occurs. Indeed, if left ventricular hypertrophy does not occur, the patient is likely to be in extreme difficulty, and unless the underlying problem can be corrected, the patient will soon die. Once again, “adverse” remodeling saves the day.

The problem is that left ventricular hypertrophy is just a description of wall thickness or mass and not of the consistency of the myocardium. An increase in the mass, number, or volume of cardiac myocytes, without an increased or defective production of collagen, is a healthy response to increased wall stress. An increase in mass or thickness due to an increase in the interstitial volume, as in amyloid aggregation, is bad news. Subtle increases in the collagen fraction contribute little to myocardial mass, but cause cardiac myocytes to expend more energy in deforming the myocardium, thus, provoking an increase in cardiac myocyte volume dissociated from the circulatory load.

**RIGHT VENTRICLE**

If pulmonary artery pressure is normal and there is no left heart disease, it appears that the right ventricle is required as no more than a conduit. However, right, rather than left, ventricular structure and function may be a more important determinant of the progression of heart failure and prognosis. This may be because right ventricular dysfunction reflects the summary effects of left ventricular systolic and diastolic dysfunction, mitral regurgitation, pulmonary hypertension, and right ventricular damage. Interestingly, right ventricular dysfunction is more common in patients with heart failure due to ischemic heart disease, despite the fact that right ventricular infarction is not commonly recognized. Tricuspid regurgitation may mask the severity of right ventricular dysfunction by off-loading into the right atrium at the low-pressure part of the stroke volume. The right ventricular free wall is thin and prone to stress-induced remodeling that might be further accentuated by left ventricular dyssynchrony.

**ATRIAS**

The atria have multiple functions. In healthy patients, they act as a low-pressure reservoir during ventricular systole, a conduit during early diastole, and they prime the ventricle with an extra volume of blood during atrial systole. Atrial dilatation is usually a sign that either the ventricular diastolic pressure is rising or there is an atrioventricular valve dysfunction, but may occasionally be due to an atrial septal defect or isolated disease of the atrial myocardium. Atrial dilatation accompanied by raised plasma concentrations of natriuretic peptides is strongly suggestive of heart failure; the echocardiogram will then determine the phenotype—presence or absence of valve disease, with or without a reduced left ventricular ejection fraction.

Atrial remodeling is an important trigger for atrial fibrillation, which is a common precipitant of heart failure. As the atria dilate, their reservoir volume increases, serving to limit any increase in atrial pressure during ventricular systole. This function may be limited by atrial hypertrophy and fibrosis that will reduce atrial myocardial compliance, partially offsetting the increase in atrial chamber compliance based on Laplace’s law. Conduit function presumably reflects ventricular compliance rather than any intrinsic atrial property. Atrial systolic ejection will be reduced by both intrinsic atrial myocardial dysfunction and rising ventricular end-diastolic pressure.
**CARDIAC INFLAMMATION**

Inflammation can cause damage and repair. Myocarditis is an ill-defined entity that appears common in some parts of the world and exceedingly rare in others. To what extent this reflects differences in perception, definition, investigation, or geography is unclear. However, there is probably always an inflammatory component to myocardial remodeling, even when it is not pathological, independently of whether it is “adverse” or not. Patients with cardiac dysfunction have increased plasma markers of inflammation (e.g., high-sensitivity C-reactive protein [hsCRP] and ST2) and fibrosis (e.g., galectin-3). Intense exercise in healthy subjects will induce inflammation in skeletal muscles and troponin release; therefore, it would be surprising not to find an inflammatory response in the myocardium. Exercise during a viral illness is known to provoke myopericarditis.

**TROPHIC FACTORS**

Hemodynamic stress, either volume or pressure, is the most important determinant of myocardial remodeling. However, this may be mediated or modified by a variety of neuroendocrine or paracrine systems. Testosterone accounts, in part, for the greater cardiac mass among men, and it may contribute to cardiac hypertrophy in response to exercise training and be amplified by exogenous use. The sympathetic nervous and renin-angiotensin-aldosterone system are also important adjuvant stimuli to cardiac hypertrophy. Blocking hypertrophic stimuli using agents, such as trastuzumab (Herceptin), may lead to the development of heart failure in susceptible individuals.

**REMODELING IN HEALTHY PATIENTS**

The heart is a highly efficient biological pump with huge functional reserves that can rapidly adapt to changes in metabolic demand. Curiously, the clinical syndrome of heart failure appears long before the contractile reserve of the heart is exhausted. Even patients with severe heart failure are able to increase cardiac output during exercise; this may reflect the importance of congestion, rather than cardiac output, on the heart failure syndrome.

Every heart experiences remodeling during growth from childhood to old age, which probably reflects cardiac myocyte proliferation, along with increases in individual cardiac myocyte volume. Pregnancy induces dramatic remodeling in a few months, which resolves rapidly after the end of the pregnancy. Exercise training to improve cardiovascular fitness will have obvious effects within a few weeks on cardiac remodeling and cardiac performance during stress. In some people, these changes are florid and may have a pathological appearance. A period of detraining may be enforced to induce resolution in an attempt to distinguish between physiological and pathological changes. To what extent these changes are a healthy response of a genetically predisposed heart is unclear.

**REMODELING AFTER MYOCARDIAL INFARCTION**

Myocardial infarction in humans is a complex process. Usually, this will involve a volume of acute myocardial necrosis and a region around the central necrosis where myocardial viability hangs in the balance and where some myocytes will eventually die and other “stunned” myocytes will recover. The rest of the myocardium is suddenly exposed to greater hemodynamic stress to compensate for the loss of infarcted myocardium and left ventricular wall dyskinesia. Contraction of uninfarcted myocardium will increase stress on the infarcted and peri-infarcted region, potentially enlarging the volume of necrosis and stretching the necrotic tissue. Eventually, inflammatory repair will digest necrotic and apoptotic myocytes and stimulate the production of interstitial collagen to create a scar. Pericardial restraint and surviving islands of myocardium and collagen help prevent scar stretch as does lowering the stress on the scar. Treatments that lower systolic and diastolic left ventricular pressures (angiotensin-converting enzyme [ACE] inhibitors and mineralocorticoid receptor antagonists [MRAs]) and agents that reduce contractility (β-blockers) or increase diastolic blood flow (β-blockers) help protect surviving myocardium and reduce its adverse impact on the developing myocardial scar. In the meantime, stunned myocardium may recover or become dormant (hibernate). Early intervention to open occluded arteries may limit infarct size and subsequent remodeling, but opening late occlusions may do more harm than good.

The net effect of this process is usually an acute increase in left ventricular volume and a reduction in contractility, followed by recovery to a varying extent after a few days or weeks due to the resolution of stunning. The left ventricle will undergo remodeling to accommodate the scar. Limiting scar stretch during scar formation may be the most important target for antiremodeling strategies after myocardial infarction.
surviving myocardium will undergo hypertrophy to compensate for the increased wall stress; however, if wall stress is reduced by effective pharmacological therapy, this may not be required. The conventional story is that once left ventricular dilatation starts, it then progresses inexorably and leads to worsening cardiac function, heart failure, and ultimately death, either through the provocation of arrhythmias or end-stage congestion. This may have been true once, but possibly, due to the benefits of modern therapy, this no longer seems to be the case for patients, although it may be in animal models. In the classic clinical studies, almost all ventricular remodeling occurred within a few weeks, with very little evidence of progressive dilatation or hypertrophy thereafter.\(^{45,51}\)

### REMODELING IN DILATEDCARDIOMYOPATHY AND CHRONIC LEFT VENTRICULAR SYSTOLIC DYSFUNCTION

Dilated cardiomyopathy usually presents as clinically overt and severe heart failure. The etiology of cardiac myocyte dysfunction is obscure, but the hypothesis that a genetically susceptible ventricle has been subjected to an acute insult, possibly viral, is attractive, although the evidence is currently inconclusive for most cases. At presentation, left ventricular dysfunction is typically severe, and the left ventricle is dilated and globular in shape with substantial and eccentric left ventricular hypertrophy. The picture usually suggests that left ventricular dysfunction has been present for weeks, months, or even years before presentation. Patients with a low mass-to-volume ratio may have a worse prognosis.\(^{52}\)

Historically, before the advent of contemporary treatments, recovery of left ventricular function was not infrequently observed, although for others left ventricular function deteriorated.\(^{53}\) Since the advent of \(\beta\)-blockers, ivabradine, and cardiac resynchronization therapy (CRT), left ventricular function now improves in the majority of patients, with few developing the need for heart transplantation. Occasionally, severe coronary artery disease may mimic a dilated cardiomyopathy, and revascularization may lead to recovery of left ventricular function.

Peripartum cardiomyopathy is a rarely recognized cause of severe heart failure that afflicts women in the last trimester of pregnancy or in the postpartum period. If this is not thwarted by death, ventricular function will recover within weeks or months, in many cases completely.

Takotsubo cardiomyopathy is another condition where rapid recovery of ventricular function is expected. These patients have a presentation mimicking anterior myocardial infarction, often with severe heart failure, despite a rather modest increase in markers of cardiac damage. Angiography reveals ballooning of the left ventricular apex. Recovery usually occurs within days. The rapid onset and offset suggests myocardial stunning and recovery rather than remodeling in the conventional sense of the term.

With current science, a consolidated myocardial scar represents irreversible damage, preventing a full recovery of ventricular function. Most patients with dilated cardiomyopathy have little or no myocardial scarring, and both spontaneous recovery and medically induced recovery are common.\(^{54}\) The goal of treatment for dilated cardiomyopathy should be first to control symptoms, then to cause remission of the disease (recovery of cardiac structure and function), and finally, to cure it (withdrawal of therapy without disease recurrence).\(^{55}\) Great strides toward the first two goals have been made in the last decade (Figure 3).\(^{56}\)

Long-term follow-up of patients with left ventricular systolic dysfunction receiving contemporary therapy reveals little evidence of progressive left ventricular dilatation. Indeed, left ventricular volumes and ejection fractions often continue improving for years after the introduction of a \(\beta\)-blocker and up to 1 year after implantation of a cardiac resynchronization device.\(^{57,58}\) It is likely that some patients show progressive ventricular dilatation, but this occurs only in a minority of patients. In some cases, this will be due to further ischemic damage to the left ventricle, and in others, it will be due to inadequate dosing or compliance with therapy, or it may reflect the genetic substrate. However, progressive, long-term left ventricular remodeling is a phenomenon that does not occur or, at least, is no longer observed in the majority of patients.

### REMODELING IN HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy is a genetically determined disease that causes histologically observable myocardial fiber disarray, usually leading to clinical features of myocardial hypertrophy.\(^{59}\) Clinical features are often absent in infancy and the phenotype usually only becomes apparent in adolescence. Whether this reflects the trophic effect of sex hormones is uncertain. Hypertrophic cardiomyopathy can be difficult to distinguish from healthy remodeling due to weight...
Cardiac remodeling: what has changed over the past 10 years? - Cleland

**Figure 3. Therapeutic interventions in pathological ventricular remodeling.**

**Abbreviations:** ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CRT, cardiac resynchronization therapy; GLP-1, glucagon-like peptide-1; ICD, implantable cardioverter-defibrillator; MRA, mineralocorticoid receptor antagonist; RAAS, renin-angiotensin-aldosterone system; TGFβ, transforming growth factor β.


**Figure 4. Pairwise comparisons of five drug classes.**

Data are pooled differences±SEM between the percentage of change for LVM (index) (left) or systolic BP (right) with the newer drug class and the percentage of change for LVM (index) or systolic BP with the older drug class (full lines). The results of individual studies are given when there are only two available comparisons (broken lines). A negative value in the direction of the arrow means that the regression is more pronounced with the newer drug class in comparison with the older drug class, and a positive value means that the regression is less pronounced with the newer drug class. The P value indicates the statistical significance; not significant (P>0.05).

**Abbreviations:** ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BB, β-blocker; BP, blood pressure; DIU, diuretic; CCB, calcium channel blocker; LVM, left ventricular mass; SEM, standard error of means.

training or other forms of exercise. In contrast to hypertrophy due to aortic stenosis or hypertension, reducing cardiac load or using neuroendocrine antagonists appear to have little effect; the hypertrophy is autonomous.

**REMODELING IN HYPERTENSION**

Concentric left ventricular hypertrophy is the hallmark of hypertension and indicates a worse outcome. However, if it did not occur, this might have severe adverse consequences for cardiac function. The severity of hypertrophy reflects the consequences of hypertension. Treating hypertension reduces hypertrophy, which markedly reduces the risk of developing heart failure.60

**REMODELING IN VALVE DISEASE**

Atrioventricular valve regurgitation may cause, or be the consequence of, ventricular dilatation. Aortic stenosis will cause ventricular hypertrophy and aortic regurgitation will result in ventricular dilatation. Timely valve replacement will reverse remodeling, but often, delayed intervention will not, indicating irreversible damage to the myocardium.61,62 The prognosis of valve disease largely reflects the impact of disease on myocardial function.

**EFFECT OF DIURETICS ON CARDIAC VOLUMES**

Consideration of the effect of diuretics on cardiac volumes puts the pharmacological interventions for cardiovascular disease into perspective. For hypertension, thiazide diuretics will reduce blood pressure, probably reduce ventricular hypertrophy (Figure 4, Table I),60,63 and improve cardiovascular outcomes. Heart failure patients with congestion will have higher ventricular and atrial volumes that will shrink when congestion is controlled with the use of diuretics.64 From a clinical perspective, this is indistinguishable from the effects of many other agents purporting to have an effect on cardiac remodeling.

**REMODELING AND ACE INHIBITORS**

ACE inhibitors reduce the conversion of angiotensin I to angiotensin II. This causes an immediate decrease in angiotensin II to very low levels. However, sustained blockade of ACE leads to an increase in renin and angiotensin I, which may overwhelm inhibition, leading to renewed production of angiotensin II. ACE inhibitors also prevent the degradation of bradykinin, which may also improve vascular function and have an antithrombotic effect. Indeed, ACE inhibitors are rather promiscuous and have effects on many other systems. In the presence of an activated renin-angiotensin-aldosterone system, ACE inhibitors will cause vasorelaxation, with little or no effect on sodium balance (many other vasodilators tend to cause sodium retention) and reduce blood pressure substantially. These effects are usually sustained despite concerns of ACE inhibition breakthrough.

**ACE inhibitor effects on hypertension**

As expected, ACE inhibitors can reduce left ventricular hypertrophy (Figure 4, Table I).60 It is uncertain whether this just reflects the reduction in arterial pressure or if there is an additional effect through the inhibition of angiotensin II production. Treatment of hypertensive patients with an ACE inhibitor combined with a thiazide diuretic, such as indapamide, leads to a striking improvement in cardiovascular outcomes, especially heart failure.65

### Table 1. Pairwise comparison of each drug class with the other classes statistically combined.

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Change in LVM (index) (%)</th>
<th>Change in systolic BP (%)</th>
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<tr>
<td></td>
<td>N</td>
<td>n</td>
</tr>
<tr>
<td>DIU</td>
<td>24</td>
<td>1399</td>
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<tr>
<td>BB</td>
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<td>2680</td>
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<td>CCB</td>
<td>44</td>
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<td>ACEI</td>
<td>49</td>
<td>2525</td>
</tr>
<tr>
<td>ARB</td>
<td>20</td>
<td>2384</td>
</tr>
</tbody>
</table>

Values are weighted means±SEM; NS, P>0.3 for all comparisons.

**Abbreviations:** ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BB, β-blocker; BP, blood pressure; DIU, diuretic; CCB, calcium channel blocker; n, number of participants; LVM, left ventricular mass; N, number of pairwise comparisons; NS, not significant; SEM, standard error of the mean.

ACE inhibitor effects after myocardial infarction

ACE inhibitors reduce morbidity and mortality after myocardial infarction especially in patients who exhibit substantial left ventricular dysfunction or heart failure.66,67 Introduced soon after a myocardial infarction, ACE inhibitors have favorable effects on left ventricular volumes and remodeling, which may simply reflect a reduction in the systolic pressure that the left ventricle is required to generate, which reduces scar stretch. If this is true, then ACE inhibitors may be required for only a few weeks after myocardial infarction, after which they may need to be continued only for patients with hypertension or substantial persistent left ventricular dysfunction.66 Evidence against this strategy is lacking. In patients with substantial left ventricular dysfunction, the rate of left ventricular remodeling is modest beyond the first few weeks after a myocardial infarction, and therefore, the impact of ACE inhibitors is also modest. (Figure 5).45,51,68,69

ACE inhibitor effects in patients with HFREF

Patients with heart failure with a reduced left ventricular ejection fraction (HFREF) usually have a dilated left ventricle with impaired myocardial contraction. HFREF with a nondilated ventricle is unusual. The etiology is usually ischemic heart disease or dilated cardiomyopathy. These patients are often younger and usually men. ACE inhibitors exert a rather modest improvement in left ventricular function, in terms of reduction in left ventricular volume, improvement in left ventricular ejection fraction, or an increase in cardiac output (Tables II-IV [page 94, 95], Figure 6 [page 96]). However, small benefits on cardiac function, possibly combined with their favorable effects on electrolyte metabolism, translate into powerful benefits on morbidity and mortality.9

ACE inhibitor effects in patients with HFPEF

Heart failure with a preserved left ventricular ejection fraction (HFPEF) is a heterogeneous group of conditions that defy simple definition, but here, the term is used to mean diastolic left ventricular dysfunction.71 Hypertension, often complicated by atrial fibrillation, is the common etiology. Compared with patients with HFREF, those with HFPEF are older, more likely to be women, and more likely to have other life-limiting comorbidities.

ACE inhibitors probably improve outcomes in HFPEF and HFREF similarly, but the evidence is weaker for HFPEF due to smaller studies and the confounding effects of non–heart failure comorbidities.71 Clinical trials concerning the effects of ACE inhibitors on ventricular function in HFPEF are sparse.72

REMODELING AND ARBs

Angiotensin receptor blockers (ARBs) inhibit the effects of angiotensin II, specifically on the angiotensin I receptor. Blocking these receptors causes a rise in an-
giotensin II, which may stimulate other receptors and lead to beneficial effects. However, increases in angiotensin II will compete with ARBs for the stimulation of the angiotensin I receptor. Hemodynamically and metabolically, the effects of ARBs and ACE inhibitors are similar. However, ARBs do not affect bradykinin or other factors metabolized by ACE.

**ARB effects on hypertension**

ARBs reduce left ventricular hypertrophy, but whether this just reflects their effect on blood pressure or an additional antitrophic effect from the reduction in angiotensin II is uncertain. As debated above, an agent that interfered with remodeling appropriate to the hemodynamic load might be deleterious. ARBs appear somewhat less effective in improving outcomes than ACE inhibitors, suggesting that bradykinin might be an important mediator of the effects of ACE inhibitors.

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**Table II. Absolute effect of drugs and devices on the change in ejection fraction compared with placebo.**

For information on the trials, please see reference 70 for complete details.

<table>
<thead>
<tr>
<th>Intervention (Ref)</th>
<th>ΔEF (95% CI)</th>
<th>Mean follow-up weeks [range]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone17,68,69</td>
<td>3.8 (-1.7 to 9.2)</td>
<td>60.7 [26-104]</td>
</tr>
<tr>
<td>Amlodipine70</td>
<td>1.9 (1.8 to 2.0)</td>
<td>12</td>
</tr>
<tr>
<td>Bisoprolol41</td>
<td>12.0 (4.4 to 19.6)</td>
<td>52</td>
</tr>
<tr>
<td>Bucindolol19,71-73</td>
<td>4.2 (3.7 to 4.7)</td>
<td>22 [12-21]</td>
</tr>
<tr>
<td>CPT74-77</td>
<td>2.7 (1.9 to 3.5)</td>
<td>21 [6-26]</td>
</tr>
<tr>
<td>Canesartan78</td>
<td>4.0 (0.5 to 7.5)</td>
<td>26</td>
</tr>
<tr>
<td>Captopril79-84</td>
<td>3.3 (0.3 to 6.4)</td>
<td>36.7 [12-21]</td>
</tr>
<tr>
<td>Carvedilol23,24,49,85-104</td>
<td>6.9 (5.8 to 8.0)</td>
<td>30 [13-21]</td>
</tr>
<tr>
<td>Digoxin84,105-109</td>
<td>2.7 (1.2 to 4.1)</td>
<td>48.3 [12-208]</td>
</tr>
<tr>
<td>Enalapril19,42,110-113</td>
<td>3.7 (1.5 to 5.9)</td>
<td>24 [4-52]</td>
</tr>
<tr>
<td>Enalapril-Prev21</td>
<td>2.0 (-0.8 to 4.8)</td>
<td>52</td>
</tr>
<tr>
<td>Enoximone114-119</td>
<td>3.4 (0.5 to 6.3)</td>
<td>8.7 [4-16]</td>
</tr>
<tr>
<td>Etapecet20</td>
<td>4.4 (3.7 to 5.1)</td>
<td>13</td>
</tr>
<tr>
<td>Felodipine43,121,122</td>
<td>4.0 (1.2 to 6.7)</td>
<td>30 [12-21]</td>
</tr>
<tr>
<td>Flosequinan123,124</td>
<td>-3.0 (-3.6 to -2.4)</td>
<td>10 [8-12]</td>
</tr>
<tr>
<td>Hydralazine-SDSN16,22</td>
<td>2.9 (0.8 to 5.0)</td>
<td>39 [26-52]</td>
</tr>
<tr>
<td>Ibopamine125</td>
<td>0.0 (-4.9 to 4.9)</td>
<td>5</td>
</tr>
<tr>
<td>Metoprolol CR39,40,126,127</td>
<td>4.5 (1.8 to 7.1)</td>
<td>25.5 [24-26]</td>
</tr>
<tr>
<td>Mibefradil44</td>
<td>0.5 (-2.8 to 3.8)</td>
<td>26</td>
</tr>
<tr>
<td>Milrinone109</td>
<td>2.2 (1.5 to 2.9)</td>
<td>53</td>
</tr>
<tr>
<td>Moxonidine128</td>
<td>4.0 (-0.5 to 8.5)</td>
<td>19</td>
</tr>
<tr>
<td>Prazosin16,129-131</td>
<td>2.5 (0.6 to 4.4)</td>
<td>28.3 [9-52]</td>
</tr>
<tr>
<td>Spironolactone132-134</td>
<td>3.0 (1.9 to 4.1)</td>
<td>25.7 [8-52]</td>
</tr>
<tr>
<td>Tolvaptan75</td>
<td>0.8 (-0.3 to 1.9)</td>
<td>54</td>
</tr>
<tr>
<td>Valsartan78</td>
<td>1.3 (0.7 to 1.9)</td>
<td>78</td>
</tr>
</tbody>
</table>

* Enalapril was examined separately when studied in patients with asymptomatic left ventricular dysfunction (LVD), as this was the only trial that exclusively examined patients with asymptomatic LVD.

† When more than one trial existed for a specific therapy, meta-analysis was used to calculate the absolute change (Δ) in ejection fraction (EF) compared with placebo (ΔEF = mean net difference in EF between intervention and placebo groups: [intervention EF – baseline] – [placebo EF – baseline], in EF % units).

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**ARB effects after myocardial infarction**

ARBs and ACE inhibitors probably exert similar effects on left ventricular function and prognosis after myocardial infarction, but the effect of ARBs may be more dose dependent.74-75

**ARB effects in patients with HFREF**

ARBs have similar effects on left ventricular function as ACE inhibitors, but again, these may be more dose-dependent effects.76,77

**ARB effects in patients with HFPEF**

There is little evidence that ARBs are clinically effective in patients with HFPEF, perhaps because few of the patients enrolled in these studies had evidence of substantial cardiac dysfunction.78 Without an accurate di-
### Cardiac Remodeling: What Has Changed Over the Past 10 Years?

Cleland

#### Table III.
Absolute Effect of Drugs and Devices on the Change in End-Diastolic Volume Compared with Placebo.

<table>
<thead>
<tr>
<th>Intervention (Ref)</th>
<th>No. of studies (n [range])</th>
<th>ΔEDV (95% CI)†</th>
<th>Mean follow-up weeks [range]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol25,41</td>
<td>2 (188 [28-160])</td>
<td>-52.5 (-108.1 to 3.2)</td>
<td>37 [22-52]</td>
</tr>
<tr>
<td>Buindolol72,73</td>
<td>2 (188 [49-139])</td>
<td>-37.1 (-75.8 to 1.6)</td>
<td>12</td>
</tr>
<tr>
<td>CRT 74,78,115</td>
<td>5 (1086 [34-490])</td>
<td>-31.8 (-33.6 to -30.0)</td>
<td>19.4 [6-26]</td>
</tr>
<tr>
<td>Candesartan79</td>
<td>1 (305)</td>
<td>-8.2 (-232.0 to -215.6)</td>
<td>26</td>
</tr>
<tr>
<td>Captopril8,81,85,89,136-138</td>
<td>7 (688 [40-298])</td>
<td>-15.4 (-19.5 to -11.4)</td>
<td>44.4 [25-52]</td>
</tr>
<tr>
<td>Carvedilol8,86,89,99,97,98,103,119</td>
<td>11 (900 [21-415])</td>
<td>-26.7 (-40.5 to -13.0)</td>
<td>29.3 [13-52]</td>
</tr>
<tr>
<td>Digoxin106,108</td>
<td>2 (266 [88-178])</td>
<td>-9.9 (-39.7 to 20.0)</td>
<td>16 [12-20]</td>
</tr>
<tr>
<td>Enalapril23,42,110</td>
<td>3 (374 [17-301])</td>
<td>-11.1 (-20.8 to -1.4)</td>
<td>30 [12-52]</td>
</tr>
<tr>
<td>Enalapril-Prev21,*</td>
<td>1 (108)</td>
<td>-5.0 (-20.0 to 10.0)</td>
<td>52</td>
</tr>
<tr>
<td>Enoximone114,115</td>
<td>2 (44 [20-24])</td>
<td>31.6 (-85.0 to 148.3)</td>
<td>10 [4-16]</td>
</tr>
<tr>
<td>Etanercept120</td>
<td>1 (47)</td>
<td>-18.0 (-22.7 to -13.3)</td>
<td>13</td>
</tr>
<tr>
<td>Felodipine43,122</td>
<td>2 (280 [20-260])</td>
<td>-52.7 (-161.8 to 56.4)</td>
<td>39 [26-52]</td>
</tr>
<tr>
<td>Hydralazine-ISDN22</td>
<td>1 (459)</td>
<td>-5.6 (-19.8 to 8.5)</td>
<td>26</td>
</tr>
<tr>
<td>Ibopamine25</td>
<td>1 (18)</td>
<td>33.9 (-43.8 to 111.5)</td>
<td>5</td>
</tr>
<tr>
<td>Metoprolol CR39,126,127</td>
<td>3 (486 [17-301])</td>
<td>-27.6 (-63.9 to 8.8)</td>
<td>24.7 [24-26]</td>
</tr>
<tr>
<td>Prazosin129,130</td>
<td>2 (45 [22-23])</td>
<td>4.1 (-50.8 to 59.1)</td>
<td>17.5 [9-26]</td>
</tr>
<tr>
<td>Spironolactone132,133</td>
<td>2 (143 [37-106])</td>
<td>-26.9 (-42.3 to -11.5)</td>
<td>34.5 [17-52]</td>
</tr>
<tr>
<td>Tolvaptan45</td>
<td>1 (240)</td>
<td>-3.4 (-9.1 to 2.3)</td>
<td>54</td>
</tr>
<tr>
<td>Valsartan48</td>
<td>1 (5010)</td>
<td>-0.0 (-1.5 to 1.4)</td>
<td>78</td>
</tr>
</tbody>
</table>

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† When more than one trial existed for a specific therapy, meta-analysis was used to calculate the absolute change (Δ) in end-diastolic volume (EDV) compared with placebo (ΔEDV = mean net difference in EDV between intervention and placebo groups: [intervention EDV – baseline] – [placebo EDV – baseline], in mL).

### Table IV.
Absolute Effect of Drugs and Devices on the Change in End-Systolic Volume Compared with Placebo.

<table>
<thead>
<tr>
<th>Intervention (Ref)</th>
<th>No. of studies (n [range])</th>
<th>ΔESV (95% CI)†</th>
<th>Mean follow-up weeks [range]</th>
</tr>
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<tr>
<td>Bisoprolol25,41</td>
<td>2 (188 [28-160])</td>
<td>-63.0 (-111.1 to -14.9)</td>
<td>37 [22-52]</td>
</tr>
<tr>
<td>CRT 74,78,115</td>
<td>5 (1086 [34-490])</td>
<td>-25.8 (-28.5 to -23.2)</td>
<td>19.4 [6-26]</td>
</tr>
<tr>
<td>Candesartan79</td>
<td>1 (305)</td>
<td>-11.3 (-222.8 to 200.1)</td>
<td>26</td>
</tr>
<tr>
<td>Captopril8,81,85,89,136-138</td>
<td>7 (688 [40-298])</td>
<td>-15.7 (-21.9 to -9.6)</td>
<td>44.4 [25-52]</td>
</tr>
<tr>
<td>Carvedilol8,86,89,99,97,98,103,119</td>
<td>9 (852 [21-415])</td>
<td>-33.9 (-48.4 to -19.3)</td>
<td>32.2 [13-52]</td>
</tr>
<tr>
<td>Digoxin108</td>
<td>1 (178)</td>
<td>-19.5 (-40.1 to 1.0)</td>
<td>12</td>
</tr>
<tr>
<td>Enalapril23,42</td>
<td>2 (351 [50-301])</td>
<td>-19.6 (-46.2 to 7.0)</td>
<td>52 [52]</td>
</tr>
<tr>
<td>Enalapril-Prev21,*</td>
<td>1 (108)</td>
<td>-5.0 (-18.6 to 8.6)</td>
<td>52</td>
</tr>
<tr>
<td>Etanercept130</td>
<td>1 (47)</td>
<td>-24.3 (-28.8 to -19.8)</td>
<td>13</td>
</tr>
<tr>
<td>Felodipine43,122</td>
<td>2 (280 [20-260])</td>
<td>-55.4 (-157.1 to 46.4)</td>
<td>39 [26-52]</td>
</tr>
<tr>
<td>Hydralazine-ISDN22</td>
<td>1 (459)</td>
<td>-8.8 (-18.4 to 0.8)</td>
<td>26</td>
</tr>
<tr>
<td>Ibopamine25</td>
<td>1 (18)</td>
<td>28.2 (-48.5 to 104.9)</td>
<td>5</td>
</tr>
<tr>
<td>Metoprolol CR39,127</td>
<td>2 (467 [41-426])</td>
<td>-30.8 (-73.4 to 11.7)</td>
<td>25 [24-26]</td>
</tr>
<tr>
<td>Prazosin129,130</td>
<td>2 (45 [22-23])</td>
<td>-4.3 (-62.2 to 53.5)</td>
<td>17.5 [9-26]</td>
</tr>
<tr>
<td>Spironolactone132,133</td>
<td>2 (143 [37-106])</td>
<td>-27.7 (-31.3 to -24.0)</td>
<td>34.5 [17-52]</td>
</tr>
<tr>
<td>Tolvaptan45</td>
<td>1 (240)</td>
<td>-5.4 (-12.2 to 1.4)</td>
<td>54</td>
</tr>
</tbody>
</table>

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agnosis, an effective treatment may appear to fail. However, even in the subset of patients with substantial cardiac dysfunction, ARBs appeared to be ineffective. Clinical evidence of an important effect on ventricular remodeling in HFPEF is sparse.

REMODELING AND ARNIS

This new pharmacological class combines an ARB with a neprilysin inhibitor (ARNI). Neprilysin, rather like ACE inhibitors, is a promiscuous enzyme that metabolizes bradykinin and many other hormones. Previous studies of agents that blocked both ACE and neprilysin suggested possible superiority over ACE inhibitors, but with a greater risk of angioedema, hence, their development was blocked. So far, ARNIs do not appear to have the same problem. In a head-to-head comparison with enalapril, an ARNI was superior and exerted a greater reduction in morbidity and mortality. Studies of its effects on ventricular function have not yet been published.

REMODELING AND MRAS

Plasma concentrations of aldosterone may increase due to greater secretion stimulated by increases in angiotensin II or reductions in serum potassium, or due to reduced degradation by the liver. Aldosterone-secreting adenomas (Conn’s syndrome) may also occur. MRAs block the effects of aldosterone on the distal renal tubule, reducing the reabsorption of sodium in exchange for potassium. The reduction in sodium may reduce circulating volume, and therefore, blood pressure and congestion. Increases in serum potassium, along with reduced congestion, may account for some of the apparent antiarrhythmic effects of MRAs.

However, the rise in serum potassium is insufficient to account for all of the potassium reabsorbed, most of which must be accommodated intracellularly. Since there is little change in intracellular potassium concentration, this implies that intracellular volume expansion occurs. Conventional diuretics may reduce intra- and extracellular volumes, whereas MRAs may correct the former and amplify the latter. The implications for cell function are unclear. Other studies suggest that MRAs have important effects on sympathetic nervous system activity and collagen metabolism, but the clinical significance of these observations is unclear.

MRA effects on hypertension

MRAs are effective antihypertensive agents that reduce left ventricular hypertrophy; however, evidence that they improve outcomes in hypertension is lacking.

MRA effects after myocardial infarction

MRAs reduce sudden death, morbidity, and mortality in patients who have sustained a myocardial infarction complicated by heart failure or substantial left ventricular dysfunction. The effect on left ventricular volume is modest and may reflect effects on blood pressure and circulating volume rather than a true effect on remodeling. Trials show that eplerenone reduces markers of collagen metabolism, suggesting that it might have an effect on extracellular matrix turnover. However, it is uncertain whether this is a direct effect or secondary to the conventional effects of MRAs.

Figure 6. Predicted probability of mortality by drug and device effects on end-diastolic volume.

Predicted probability of a categorical mortality outcome based on drug and device effects on EDV; the lines represent the likelihood of a categorical mortality outcome based on an intervention’s trial-level effect on EDV compared with placebo (unadjusted, weighted, ordered logistic regression). Color-coded mortality effect based on data from mortality trials. Each data point represents a placebo-corrected change in EDV from an individual remodeling trial plotted against the mortality odds ratio for the specific therapy. The graph suggests that if the mean change in EDV is -10 mL in the short-term studies, the probabilities that the long-term mortality studies will be significantly favorable (blue line), neutral (black line), and significantly unfavorable (red line) is approximately 56%, 43%, and 1%, respectively.

Abbreviations: EDV, end-diastolic volume; EF, ejection fraction.

Studies investigating persistence of these effects after withdrawal of MRAs have not yet been conducted.

**MRA effects in patients with HFREF**

MRAs reduce morbidity and mortality in patients with HFREF and reduce the incidence of atrial fibrillation. MRAs reduce left ventricular volumes, increase left ventricular ejection fraction, and have favorable effects on natriuretic peptides and markers of collagen metabolism, but whether their effects persist when treatment is stopped is uncertain. The impact of MRAs may only reflect their hemodynamic effects.

**MRA effects in patients with HFPEF**

In a large multicenter study, spironolactone reduced morbidity and mortality in patients with HFPEF and increased plasma concentrations of natriuretic peptides, but overall, the study was neutral due to the inclusion of many low-risk patients who probably did not have substantial cardiac dysfunction. This is yet another warning not to rely on cardiac imaging alone when selecting patients for studies on HFPEF, and the importance of excluding low-risk patients with normal plasma concentrations of natriuretic peptides. Spironolactone improves diastolic left ventricular function and reduces plasma concentrations of natriuretic peptides in patients with mild HFPEF.

**REMODELING AND β-ADRENERGIC RECEPTOR BLOCKERS (β-BLOCKERS)**

Sympathetic nervous system activation will cause vasoconstriction and bronchodilation, an increase in blood pressure, myocardial contractility, and heart rate, and a decrease in serum potassium. Long-term activation may cause myocardial hypertrophy and cardiac myocyte damage. β₁-adrenergic receptors are widespread in the cardiovascular system and their blockade is probably responsible for most of the actions of this class of agents. β₂-adrenergic receptors are found in the airways, where they mediate bronchodilation. Stimulation of β₁-adrenergic receptors also drives potassium into cells and may cause hypokalemia. Stimulation of β₂-adrenergic receptors causes vasoconstriction and long-term myocardial hypertrophy. The role of β₂-adrenergic receptors in human disease is uncertain. β-Blockers differ in their receptor selectivity and lipophilicity, which affects their incorporation into cell membranes and may lead to different effects. Some agents are partial agonists, which appear to have deleterious effects; such agents should generally be avoided.

**β-Blocker effects on hypertension**

Most studies of β-blockers on hypertension have been conducted with atenolol, but it is not clear whether this agent improves clinical outcomes in hypertension. Other agents that are nonselective or lipophilic or both may be superior. β-Blocker studies, mainly using atenolol, suggest that they may not reduce left ventricular hypertrophy as much as other drug classes, such as ARBs.

**β-Blocker effects after myocardial infarction**

Nonselective β-blockers have consistently reduced morbidity and mortality after myocardial infarction; however, the evidence for β₁-selective agents is less compelling. There is a strong clinical impression that β-blockers may reduce infarct size, hasten recovery from myocardial stunning, and reduce left ventricular remodeling after myocardial infarction, but there is a remarkable lack of evidence from controlled trials.

**β-Blocker effects in patients with HFREF**

There is overwhelming evidence that β-blockers improve outcomes in patients with heart failure if they are in sinus rhythm. Whether this is due to a reduction in heart rate or adrenergic receptor blockade is uncertain. Agents that reduce sympathetic nervous system activation increased mortality in heart failure patients, which could be interpreted as evidence that heart rate is the key target of β-blockers. However, excessive reductions in blood pressure may have been responsible for the adverse effect of moxonidine on outcomes. Ivabradine, a sinus node inhibitor that does not affect adrenergic receptors, may exert similar effects as β-blockers on outcomes for patients in sinus rhythm. Curiously, β-blockers do not improve outcomes in patients with atrial fibrillation despite reducing the ventricular heart rate. This might reflect excessive nocturnal bradycardia, which could trigger pause-dependent ventricular arrhythmias.

β-Blockers can cause a dramatic improvement in left ventricular function with restoration of normal ventricular volumes and ejection fractions (cardiac remission). This is often observed in patients with dilated cardiomyopathy, but also in patients with ischemic heart disease who have a large volume of myocardium affected by ischemia or hibernation. β-Blockers cannot restore function to the myocardial scar, which is why patients with heart failure due to ischemic heart disease are less likely to have dramatic improvements...
in ventricular function after myocardial infarction than those with dilated cardiomyopathy. This shows the importance of knowing about the myocardial substrate when assessing the effects of treatments on ventricular remodeling. Sadly, few studies make this effort. Although patients with ischemic heart disease are less likely to improve their left ventricular function with β-blockers, ischemic heart disease does not diminish the effect of β-blockers on prognosis. This is one of several examples showing that the effects of treatment on ventricular remodeling are dissociated from their effects on prognosis.84

β-Blocker effects in patients with HFPEF

Studies of β-blockers on HFPEF are confounded by the high prevalence of atrial fibrillation. When analysis is confined to those patients in sinus rhythm, β-blockers may be effective88; however, their effects on diastolic function are complex.99 Slowing heart rate allows a longer period for ventricular filling, which may be beneficial when the problem is slow myocardial relaxation. However, β-blockers slow myocardial relaxation, and therefore, this may obviate some of their benefits. If the diastolic problem resembles that of a restrictive cardiomyopathy, a longer filling period could be deleterious and just lead to higher end-diastolic pressures. Ultimately, any benefit of β-blockers might be related to the reduction in blood pressure, ischemia, and arrhythmias rather than to cardiac remodeling or improved diastolic function.

REMODELING AND IVABRADINE

Ivabradine is a first-in-class sinus node inhibitor. Its sole mode of cardiovascular action is thought to be mediated through slowing sinus node discharge, and therefore, heart rate. It is not an antihypertensive agent and has not been studied in the setting of acute myocardial infarction. Among patients with stable angina, ivabradine may increase cardiovascular risk, but in patients with a reduced left ventricular ejection fraction and a resting heart rate >70 beats per minute (bpm), it reduces cardiovascular risk.

Ivabradine effects in patients with HFREF

Among patients with sinus rhythm and a heart rate >70 bpm, ivabradine reduces adverse outcomes, and when heart rate exceeds 75 bpm, it reduces mortality. The effects are greater in younger patients and those with dilated cardiomyopathy. Ivabradine reduces ventricular volume and increases left ventricular ejection fraction. The increase in left ventricular ejection fraction is proportional to the reduction in heart rate, and surprisingly, it is similar in patients with or without ischemic heart disease,100 despite the above concerns about the myocardial scar limiting the ability of the left ventricle to recover. However, in younger patients with dilated cardiomyopathy, dramatic improvements in ventricular function may be observed.101

Ivabradine effects in patients with HFPEF

There are few data on ivabradine for patients with HFPEF, but the existing data are positive. Studies suggest that ivabradine has favorable effects on diastolic function compared with either placebo or bisoprolol.71

OTHER PHARMACOLOGICAL AGENTS

The above pharmacological agents reflect the cornerstones of therapy for heart failure. Calcium channel blockers are less commonly used for heart failure, but may have favorable effects on left ventricular hypertrophy and outcomes in patients with hypertension.102

REMODELING AND CRT

CRT effects in patients with HFREF

The effects of CRT have only been studied in patients with HFREF. The cardiac response to CRT is biphasic. Successful implantation of CRT leads to an immediate reduction in systolic and diastolic mitral regurgitation (if present) and an improvement in left ventricular ejection fraction, leading to an increase in systolic blood pressure.58 The increase in systolic blood pressure presumably reflects an increase in cardiac power generation and it has been used as an indicator of whether effective CRT has been delivered. Thus, much of the benefit of CRT is delivered within a few seconds. Subsequently, and perhaps consequent to these early benefits, there is a more gradual secondary phase of remodeling, with shrinking ventricular volumes and improvements in the left ventricular ejection fraction. Most of this secondary phase is complete by 9 months with little change thereafter.58 CRT has little effect on right ventricular remodeling or function.103 Unfortunately, it is far from clear how important CRT-induced cardiac remodeling is to the effects of CRT on prognosis.104 Observational trials are confounded by the lack of a control group. A patient might have a good outcome after CRT implantation, but their prognosis might have been good anyway.105 With few exceptions, a randomized controlled trial is required to distinguish the effects.
of an intervention from the natural history of the disease. The remodeling effects of CRT are consistently and strikingly greater in patients with dilated cardiomyopathy than in patients with ischemic heart disease, as myocardial scar limits the ability of the left ventricle to undergo remodeling. However, CRT exerts similar benefits on outcome, especially mortality, in patients with or without ischemic heart disease.

**CONCLUSION**

Remodeling of the atrial and ventricular myocardium is a necessary consequence of important cardiovascular disease, but in many respects, it is a consequence and not the cause. There is no doubt that atrial and ventricular hypertrophy and dilatation are associated with worse outcomes. Effective treatment of causal factors will cause “reverse” remodeling, which is generally associated with better outcomes. However, this is a generalization. Due to myocardial scarring, patients with ischemic heart disease are less likely to have marked improvements in left ventricular function, and yet, there is no diminution in the effects of many treatments on prognosis. Therefore, remodeling is only one factor determining the response to treatment. Moreover, treatments directed at remodeling, rather than the disease causing the remodeling, may have an adverse impact on outcomes. Finally, it would appear that modern pharmacological therapy is effective in preventing progressive “adverse” remodeling and aids recovery of ventricular function in many patients. Remodeling is best viewed as a barometer or symptom of the effect of disease on the heart, rather than a target for treatment in its own right.

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Remodeling: What Has Changed Over the Past 10 Years?

Expert Answers to Three Key Questions

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What role does intracellular and intercellular signaling play in cardiac remodeling?

Paola Rizzo, PhD1; Pietro Ameri, MD, PhD2

1Department of Morphology, Surgery, and Experimental Medicine and Laboratory for Technologies of Advanced Therapies (LTTA) - University of Ferrara - Ferrara - 44121 - ITALY
2Research Center of Cardiovascular Biology - Department of Internal Medicine - University of Genova - Genova - 16132 - ITALY

Pathological cardiac remodeling leads to progressive worsening of cardiac function and heart failure. Novel and more effective therapeutic strategies are needed to slow down or reverse this often fatal process. The dissection of the molecular events underlying cardiac remodeling could lead to the identification of promising new candidates for targeted treatment of heart failure. In this review, we discuss the role of the Notch and Akt (protein kinase B) signaling pathways in mediating intercellular and intracellular events that play an important role in the myocardium under physiological and pathological conditions, including remodeling.

Pathological cardiac remodeling is a complex series of transcriptional, structural, electrophysiological, and functional events occurring within the myocardium. It is a response of the heart, especially the left ventricle, to pathophysiological stimuli, such as ischemia and reperfusion or excessive mechanical load. Remodeling confers short-term benefits; however, in the end, it is maladaptive and leads to progressive worsening of cardiac function and heart failure (HF). Current therapies, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonists, and β-adrenergic receptor blockers (β-blockers), only partially halt cardiac remodeling.

The extent of left ventricle remodeling is dictated by an intricate combination of intercellular interactions and intracellular events, including cardiomyocyte death (through necrosis, apoptosis, or autophagy) and hypertrophy (in response to ventricle stretching and neurohormonal activation). Furthermore, fibroblasts, vascular smooth muscle cells, endothelial cells, and leukocytes are also involved in the remodeling process by promoting fibrosis, vascular stiffness, endothelial dysfunction, deregulated angiogenesis, and inflammation. Recent papers have comprehensively reviewed the intercellular and intracellular signaling networks chiefly implicated in cardiac remodeling.1-3 Here, we will focus on the Notch and Akt (protein kinase B) signaling pathways. The former has long been “off the beaten track” in cardiovascular science and is only now emerging as a promising therapeutic target to reduce myocardial damage. Conversely, the scientific literature about Akt signaling in the heart is vast; nevertheless, the more this signaling mediator is studied, the more researchers realize that the achieved knowledge is approximate and that many aspects of Akt activity and regulation remain to be elucidated. In recent years, important insights into both the Notch and Akt signaling pathways have been acquired, although for different reasons. This article will provide an updated overview of the role of Notch and Akt signaling in cardiac remodeling and discuss the cross-talk between these two pathways.

NOTCH SIGNALING PATHWAY: A MAJOR MEDIATOR OF INTERCELLULAR COMMUNICATION

Fundamentals of Notch signaling

The Notch signaling pathway is an ancient signaling system of communication between adjacent cells.4 Humans have four Notch receptors (Notch1-4) and five ligands (Delta-
What role does intracellular and intercellular signaling play in cardiac remodeling?

The Notch signaling pathway plays a major role during heart development,9 and consistently, mutations in components of the Notch signaling pathway have been identified in human congenital defects, such as Alagille syndrome, bicuspid aortic valve disease, calcification of the heart valve,10 and more recently, left ventricular noncompaction cardiomyopathy.11 Notch dysregulation, without a known genetic cause, has also been linked to cardiac disease.

In patients with symptomatic aortic stenosis12 and in HF patients with high circulating levels of secreted frizzled-related protein 3 (Sfrp3), a protein able to inhibit Notch signaling, the circulating levels of the Notch ligand DLL1 are elevated and associated with mortality.13,14 More recently, a phase 1 dose escalation and expansion study of the anticancer stem cell agent demcizumab, an antibody against the Notch ligand DLL4 that interferes with tumor angiogenesis, has shown that prolonged administration of this antibody is associated with an increased risk of congestive HF.15 These studies show that active Notch signaling is required, even in the postnatal myocardium.

In the adult rat myocardium, Notch signaling is absent under normal physiological conditions, but it becomes transiently reactivated in the myocardial infarction border zone.16 Expression of Notch signaling components has also been observed in biopsies taken from the myocardium of HF patients.17 These observations suggest a role for Notch signaling, especially in the repair of a damaged or overloaded myocardium. This hypothesis is supported by studies in animal models, in which inhibition of Notch signaling increases the size of the infarct.
scar\textsuperscript{18} and activation of Notch\textsubscript{1} signaling in cardiomyocytes results in reduced myocardial damage following an ischemic insult.\textsuperscript{19} Activation of Notch signaling has been identified as one of the molecular mechanisms by which preischemic and postischemic conditioning reduce ischemia-reperfusion damage.\textsuperscript{20,21} Similarly, the treatment with high mobility group box chromosomal protein 1 (HMGB1), a nuclear protein that acts as a cytokine when released by necrotic and inflammatory cells, promotes heart repair by activating Notch.\textsuperscript{22}

In the following paragraphs, we will describe the recent literature on the biological processes and molecular mechanisms by which Notch signaling exerts this protective role in the myocardium.

The important role played by Notch in the protection of cardiomyocyte survival has been reported by several authors. In cardiomyocytes grown under hypoxic conditions, Notch\textsubscript{1} activation leads to increased expression of antiapoptotic genes,\textsuperscript{24} whereas pharmacological inhibition of Notch signaling causes increased apoptosis.\textsuperscript{19} In a rat model of myocardial infarction, Notch\textsubscript{1} is reactivated in cardiomyocytes near the border with the infarct zone, and in the same cardiomyocytes, activation of the prosurvival Akt pathway has been observed.\textsuperscript{6} Similarly, in mice genetically modified to express the active form of Notch\textsubscript{1} in cardiomyocytes, a decreased number of apoptotic cells following myocardial infarction have been found.\textsuperscript{19} Recent work has shown that reduction in cardiomyocyte apoptosis linked to Notch activation is part of the molecular mechanism by which ischemic preconditioning and postconditioning exert their cardioprotective activity in an infarcted heart of the rat.\textsuperscript{25} Both during apoptosis and hypertrophy, the activation of Notch in cardiomyocytes is mediated by Jagged\textsubscript{1}, which is present on the surface of adjacent cardiomyocytes.\textsuperscript{23}

**Notch signaling in cardiomyocyte hypertrophy and survival**

Apoptotic death of cardiomyocytes and the subsequent hypertrophic response in the remaining cardiomyocytes are among the hallmarks of the myocardium in HF patients. The data linking Notch signaling to the regulation of cardiomyocyte hypertrophy are still scarce. One study on cardiac remodeling, secondary to hemodynamic overload due to hypertension, has shown that activation of Notch\textsubscript{1} signaling in cardiomyocytes limits the hypertrophic response, and consistently, treatment with Notch inhibitors leads to exacerbated cardiac hypertrophy, altered function, and increased mortality rate by reduced adaptation to the increased load.\textsuperscript{23}

**Notch signaling in cardiac stem cells**

The presence of cardiac precursor cells (CPCs) in the myocardium has been reported by several authors.\textsuperscript{23,26,27} CPCs expressing the stem cell factor receptor (c-kit) and stem cell antigen-1 (Sca-1) markers are self-renewing and have the potential to differentiate into cardiomyocytes, endothelial cells, and vascular muscle cells.\textsuperscript{27} The number and function of these cells are affected by age and pathological states, such as HF.\textsuperscript{28} There is growing evidence suggesting that CPCs can contribute to myocardial repair, but the re-
search in this field is still very controversial. Specifically, the number of new cardiomyocytes that can be generated by CPC differentiation greatly varies between laboratories.\textsuperscript{27,29} Furthermore, it has been shown that these cells have a temporarily limited ability to differentiate into cardiomyocytes, thus questioning their ability to repair the damaged myocardium.\textsuperscript{30} Notch is one of the pathways involved in the regulation of the stem cell niche and tightly controls their proliferation and differentiation.\textsuperscript{31}

Elegant work by Boni et al\textsuperscript{18} has shown that Notch1, present on the cell membrane of CPCs, is activated by Jagged1, which is exposed on the surface of adjacent cardiomyocytes. This activation induces the transcription factor Nkx2.5, which is involved in the expression of cardiomyogenic transcripts and the inhibition of vascular cell markers.\textsuperscript{18} Therefore, Notch1, by maintaining CPCs in a highly proliferative state and by favoring their myocyte lineage specification, regulates the pool of transit-amplifying myocytes and controls heart homeostasis and adaptation to pathological states. Consistent with this model, Notch inhibition in newborn mice induces dilated cardiomyopathy by causing a 56\% reduction in the number of cardiomyocytes.\textsuperscript{32} In a mouse model of myocardial infarction, inhibition of Notch signaling decreases Nkx2.5-positive cells and reduces the generation of new myocytes.\textsuperscript{18} Exogenous administration of HMGB1 to the mouse heart during acute myocardial infarction promotes cardiogenesis by Notch-mediated activation of CPCs.\textsuperscript{33} The role of Notch activation in controlling the differentiation of CPCs has been confirmed in a study utilizing transgenic mice overexpressing Jagged1 on cardiomyocytes. In these mice, Notch activation favored the differentiation of CPCs into Nkx2.5-positive CPCs rather than toward fibrosis-causing myofibroblasts, thereby, leading to reduced pathological remodeling and improved cardiac function compared with wild-type animals.\textsuperscript{34}

The role of Notch signaling in the regulation of the fibrotic response has been reported by other authors. Russell et al have shown that Notch-activated epicardial-mesothelial cells delaminate into the subepicardial space and undergo epithelial-mesenchymal transition (EMT) to produce a multipotent stromal cell capable of differentiating into fibroblasts.\textsuperscript{35} Notch signaling also influences the cell fate decisions of cardiomyocytes: myocardial Notch has been shown to affect the transcriptome and cellular electrophysiology of the cardiomyocytes of newborn mice to resemble cells of the specialized conduction system, suggesting that Notch can reprogram cardiomyocytes to a specialized conduction-like phenotype.\textsuperscript{36} Cardiac stem cells may be generated in the heart, or they could originally be residents in the bone marrow and be supplied to the heart by systemic circulation following ischemic damage. Bone marrow-derived endothelial precursor cells (EPCs) and mesenchymal cells (MSCs) are elevated in the blood of patients with a myocardial infarction or congestive HF.\textsuperscript{37-39} These cells participate in endothelial repair and neovascularization of ischemic organs, but they could be involved in myocardium regeneration since they have been shown to differentiate in vitro toward a cardiomyogenic phenotype.\textsuperscript{40} Coculture experiments of EPCs with Jagged1-expressing cardiomyocytes have shown that activation of Notch1 is necessary for the expression of cardiomyocyte markers in these cells. Additionally, deletion of Notch1 in bone marrow-derived MSCs impairs their recruitment, proliferation, and survival, leading to a decreased ability to repair the damaged myocardium compared with MSCs with a functional Notch1 signaling pathway.\textsuperscript{41} Activation of Notch1 signaling in bone marrow-derived MSCs by soluble Jagged1 increases their differentiation rate into cardiomyocytes in vitro.\textsuperscript{42} Conversely, activation of Notch1 in immature cardiomyocytes by Jagged1 on MSCs enhances their proliferation.\textsuperscript{43} These findings show that the functionality of the Notch pathway is essential for the repair function of these cells and that Notch signaling in stem cells obtained from patients should be evaluated before attempting to use them for therapeutic purposes. We have shown that the number of MSCs obtained from the adipose tissue of patients with severe HF is very low compared with healthy subjects. Additionally, these cells express low levels of Notch1 and Jagged1, which could hamper their ability to efficiently repair the damaged myocardium.\textsuperscript{44}

**Notch signaling in cardiac vasculature**

Notch receptors 1, 2, and 4 and Notch ligands Dll1, Dll4, Jagged1, and Jagged2 are all expressed in the endothelium, where Notch signaling controls angiogenesis and protects endothelial cells from dysfunctions caused by inflammatory cytokines, ischemia, and turbulent blood flow.\textsuperscript{45} Notch signaling also modulates proliferation, survival, and function of smooth muscle cells in the vascular wall.\textsuperscript{46} Activation of Notch signaling has been shown to occur in the endothelial and vascular muscle cells of...
cardiac vessels. In a mouse model of myocardial infarction, Notch signaling was activated by a Notch1-biding antibody that reduced scar tissue and improved cardiac function 4 weeks after infarction. This improvement was associated with increased levels of angiogenesis markers, such as smooth muscle α-actin and the endothelial marker isolectin B2. The role of Notch signaling in promoting myocardial angiogenesis has been recently confirmed by a study in which upregulation of Notch signaling has been observed in response to VEGF treatment of chronic myocardial ischemia. In a different study, treatment with MSCs modified with miR-126, a specific endothelial microRNA (miRNA), enhances angiogenesis in ischemic myocardium by releasing angiogenic factors and activating the Notch ligand Dll4.

In experimental postinfarction settings, both cardiac and pulmonary vascular endothelial dysfunctions have been shown to contribute to the development and progression of HF. Postinfarction and HF conditions are characterized by elevated levels of inflammatory cytokines, which lead to a dysfunctional endothelium by reducing the expression of endothelial nitric oxide synthase (eNOS), inducing expression of adhesion proteins, and causing endothelial cell apoptosis. A recent study by Schober et al has shown that treatment with miRNA-125 results in upregulation of Notch signaling in the endothelium of dyslipidemic mice, which promotes the repair of the damaged endothelium induced by dyslipidemia. In a different study, Notch1 activation has been linked to inhibition of the expression of miR-155, a miRNA associated with eNOS reduction. There are no available data linking Notch activation to the reduction in endothelial dysfunction in HF.

Considering its multiple effects on the vasculature, it is possible to speculate that Notch signaling could protect the damaged myocardium not only by promoting angiogenesis, but also by reducing endothelial cell dysfunctions.

**Cross-talk between Notch and other crucial signaling pathways involved in remodeling**

The progression of myocardial infarction to HF is determined by the balance between the proinflammatory response, which is needed to clear the debris caused by extensive cardiomyocyte death, and the following fibrotic response, which fills the empty space created by the necrotic tissue. For proper healing, the two responses need to be carefully orchestrated and it has been suggested that the imbalance between these two processes is a strong determinant in the pathophysiology of HF. Dying and surviving cardiomyocytes, endothelial cells, resident cardiac fibroblasts, resident mast cells, and newly recruited neutrophils, monocytes, and platelets participate in the postinfarction inflammatory response.

In the infarcted myocardium, transforming growth factor β (TGFβ) in cardiomyocytes suppresses the synthesis of a protective, anti-inflammatory response, and promotes fibrosis by enhancing fibroblast to myoblast and mesenchymal to endothelial cell transition and by modulating the activity of macrophages and other cells of the immune system. Notch is an important modulator of inflammation, even though it has opposite effects depending on the context. Notch activation has anti-inflammatory functions in the endothelium, but favors proinflammatory responses in macrophages. The use of Notch inhibitors has been shown to reduce the inflammatory response in animal models of atherosclerosis and stroke. Cross-talk between Notch and TGFβ signaling has been described in cardiac fibroblasts. Since both inflammation and TGFβ signaling are being investigated as therapeutic targets for HF, the role of Notch in this context should be carefully evaluated.

**AKT PATHWAY: THE CENTER OF INTRACELLULAR SIGNALING NETWORKS**

By regulating cardiomyocyte growth, proliferation, survival, contractility, metabolism, and secretion of autocrine and paracrine factors, Akt plays a pivotal role in maintaining the homeostasis of the heart. Altered Akt signaling has also been implicated in cardiac disease. Here, we will briefly review the aspects of Akt biology that are relevant to cardiac remodeling.

**Fundamentals of Akt signaling**

The serine/threonine kinase Akt, or PKB, is central to a variety of intracellular signaling networks. In mammals, there are three isoforms of Akt—Akt1/PKBα, Akt2/PKBβ, and Akt3/PKBγ—that each contain a pleckstrin homology (PH) domain at the amino terminus, a kinase domain, and a regulatory tail containing a hydrophobic motif at the carboxy terminus. In basal conditions, Akt is kept inactive by an interaction between the PH and kinase domains. Class I phosphoinositide-3 kinase (PI3K) is recruited to the plasma membrane by three types of ligand receptors: (i) tyrosine kinase receptors, such as the insulin-like growth factor 1 receptor (IGF-R1) and the insulin receptor, which may...
act directly or via adaptor proteins like insulin receptor substrate (IRS)-1 (Figure 2); (ii) receptors that are functionally linked to tyrosine kinases, such as glycoprotein 130; and (iii) G protein-coupled receptors, such as α- and β-adrenoreceptors.

Once activated, class I PI3K phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP2), a membrane-bound phosphoinositide, to produce phosphatidylinositol 3,4,5-trisphosphate (PIP3). The production of PIP3 is opposed by PTEN (phosphatase and tensin homolog deleted on chromosome ten), an important tumor suppressor gene.60 By binding the PH domain, PIP3 then engages Akt at the plasma membrane, where it can be phosphorylated at Thr308 of the kinase domain by another PH domain-containing kinase—phosphoinositide-dependent kinase-1 (PDK1).61 This is followed by a second phosphorylation at Ser473 of the hydrophobic motif, after which, Akt becomes fully active and can phosphorylate several substrates.62 In both cardiomyocytes16 and leukemic T cells,63 Notch signaling leads to the repression of PTEN expression, thus increasing the amount of PIP3 available to activate Akt (Figure 2).

PI3K/Akt signaling also induces the transcription factor Hes1, suggesting a bidirectional positive feedback between Notch and Akt.16 In fact, Notch activation coincides with that of Akt in the infarcted myocardium.16 Akt targets may colocalize at the plasma membrane, but are also in the cytoplasm and organelles, such as the Golgi apparatus, mitochondria, and nucleus, where Akt can translocate.64 PI3K and PDK1 may also be found in the nucleus of cardiomyocytes, suggesting the existence of a nuclear PI3K/Akt pathway, besides the canonical one where Akt accumulates in the nucleus after being activated at the plasma membrane by the PI3K-generated PIP3.65

**Akt signaling in cardiomyocytes**

The mammalian target of rapamycin (mTOR) kinase in the mTOR complex 1 (mTORC1) is one of the most extensively investigated targets of Akt (Figure 2). mTOR is normally inhibited by tuberous sclerosis 2 (TSC2). Akt phosphorylates TSC2, which disinhibits mTOR; mTORC1, in turn, phosphorylates a number of downstream proteins, including S6 kinase 1 and eukaryotic translation initiation factor 4E–binding protein 1, eventually stimulating ribosomal biogenesis and protein translation.62 Protein synthesis is further promoted by Akt, and protein catabolism is decreased, which occurs through the inhibition of the Foxo family of fork-head transcription factors and glycogen synthase kinase 3β. These events drive cardiomyocyte hypertrophy.

Akt-induced cardiac hypertrophy has been associated with enhanced contractility. At the single cardiomyocyte level, Akt has been shown to favorably modulate key components of the calcium-handling machinery, like sarcoendoplasmic reticulum calcium (2+) ATPase (SERCA2a),66 L-type calcium channels,67 and phospholamban,68 leading to improved calcium transients.
Over the last decade, the concept has emerged that the effects of Akt in the mitochondria and nucleus of cardiomyocytes may be as important as those mediated by historically investigated membrane and cytosolic substrate molecules. For instance, the established cardioprotection conferred by Akt against hypoxia in vitro and ischemia in vivo may be partly ascribed to the prevention of mitochondrial permeability transition pore opening, which causes cardiomyocyte death.

Shiraishi et al demonstrated that nuclear overexpression of Akt in cardiomyocytes also counteracts hypoxia and ischemia-reperfusion injury. In addition, this overexpression results in more efficient calcium reuptake by the sarcoplasmic reticulum, with enhanced cardiomyocyte contraction and relaxation and greater proliferation of CPCs, which release higher amounts of paracrine factors, although nuclear Akt overexpression has an impaired capacity for lineage commitment.

In the heart, like other organs, the Akt pathway is tightly controlled by regulatory feedback loops. For instance, kinases downstream of IGF-R1 or the insulin receptor induce serine phosphorylation of IRS-1; therefore, IRS-1 undergoes degradation and PI3K/Akt activation is diminished.

**Akt signaling in cardiac remodeling**

Research links the PI3K/Akt pathway to compensated cardiac hypertrophy, which is characterized by myocyte enlargement, with augmentation of both glycolysis and fatty acid oxidation, no expression of fetal genes, no fibrosis, and preserved or even augmented contractile function. Compared with wild-type mice, the hearts of mice lacking the regulatory subunits of class IA PI3K or overexpressing a dominant negative form of PI3K, are smaller and exhibit attenuated Akt signaling. However, cardiac dimensions are increased following cardiomyocyte-specific overexpression of activated PI3K. Besides confirming that Akt is downstream of PI3K, these results indicate that PI3K/Akt mediate a physiological growth of the heart. As the PI3K/Akt pathway is elicited by insulin via the insulin receptor tyrosine kinase, it has been proposed that it represents a signaling nexus for the coordination of cardiac growth, and overall body growth, as a function of the nutritional status of the organism.

After postnatal growth is concluded, the human heart can again undergo physiological hypertrophy during pregnancy or in response to exercise. The IGF-R1/PI3K/Akt signaling cascade is chiefly involved in this process. Although some discrepancies exist, possibly related to the use of different strains, aerobic training has been reported to upregulate myocardial IGF-1 in mice and rats. In addition, earlier studies found a positive correlation between circulating IGF-1 levels and maximal aerobic capacity or leisure time activity in healthy individuals. Nevertheless, the most compelling evidence comes from the analysis of transgenic mouse models, in which harmonic cardiac remodeling, resembling hypertrophy induced by pregnancy or exercise in humans, has been observed after selective overexpression of IGF-R1, PI3K, or Akt in cardiomyocytes. Enhanced systolic function has also been described in some cases. Studies based on a conditional transgenic system of inducible Akt activation in the heart have revealed that, besides increasing cardiac mass, Akt stimulates coronary angiogenesis through upregulated expression and secretion of pro-angiogenic mediators in cardiomyocytes. As a consequence, the cardiac tissue and the coronary circulation grow in parallel, in a coordinated way. On the other hand, endothelial cells release factors, such as neuregulin-1β, which stimulates Akt activity, and subsequently, hypertrophy in cardiomyocytes.

Class IA PI3K has been related to balanced cardiac remodeling, while class IB PI3K (also referred to as PI3Ky) has been implicated in pathological hypertrophy, for instance, secondary chronic ß-adrenergic receptor stimulation. Moreover, there are features of physiological remodeling that are induced by PI3K, but not Akt, such as the upregulation of ion channel subunits, which may help avoid abnormalities in myocardial excitability, or the increase in fatty acid oxidative capacity. The cellular mechanisms responsible for these Akt-independent effects of PI3K remain to be pinpointed.

In addition to promoting harmonious cardiac hypertrophy, Akt appears to oppose maladaptive remodeling. Knocking down Akt makes cardiomyocytes resistant to hypertrophy initiated by IGF-1, but sensitized to nonphysiological protein synthesis triggered by endothelin-1, and the heart of Akt−/− mice fails to achieve hypertrophy upon swim training. Conversely, pathological remodeling in response to transverse aortic constriction is exacerbated in these animals, which is consistent with the loss of the protective activity of Akt. Experimental data also suggest that Akt might limit the deterioration of contractile function once compensatory mechanisms have been exhausted.
activated in failing hearts awaiting transplantation, but not in organs with compensated hypertrophy. Surprisingly, nuclear overexpression of Akt alone does not affect cardiac tissue composition or structure, but counteracts pathological remodeling, further substantiating the paradigm that distinct functions correspond to different subcellular locations of Akt.

Against this background, it has been postulated that activation of PI3K/Akt signaling partly accounts for the benefit of aerobic exercise in HF. Indeed, swimming increases the abundance of the class IA PI3K subunit p110α, potentiates the phosphorylation of Akt and mTOR, improves cardiac remodeling, and attenuates HF in Dahl salt-sensitive hypertensive rats.

**CONCLUSIONS AND TRANSLATIONAL IMPLICATIONS**

HF is still among the leading cause of death worldwide. Following the disappointing results shown by clinical trials that failed to improve cardiac function by intracoronary injection of stem cells, the hope now lies in the in vivo delivery of cytokines or growth factors as a promising tool to enhance the regenerative potential of the heart, as well as identifying novel therapeutic targets. There is a cross-talk between the Notch and Akt signaling pathways, with the majority of the molecular pathways and biological processes involved in pathological remodeling. These two pathways are frequently activated in cancer and are being investigated in clinical trials, individually and in combination.

Studies in animal models have shown that Notch activation can reduce the extent of pathological

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**Figure 3. Notch signaling as a therapeutic target for left ventricular remodeling.**

By mediating the interactions between adjacent cells, Notch controls fibrous tissue deposition, cardiac hypertrophy, angiogenesis, and inflammation; therefore, it could represent a therapeutic target for the reduction in left ventricular remodeling. This figure summarizes the cellular functions modulated by Notch signaling in the myocardium.

**Abbreviations:** CPC, cardiac progenitor cells; Ly, leukocytes; Ma, macrophages; Mo, monocytes.

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**Figure 4. Cardiac phenotypes induced by transgenic overexpression of Akt in mouse models.**

To a certain extent, increased activity of Akt results in balanced remodeling with preserved or even enhanced function, resembling human physiological hypertrophy. By contrast, excess or sustained Akt activation causes pathological remodeling.

**Abbreviation:** Akt, protein kinase B.
remodeling and improve cardiac function (Figure 3). Since Notch can also promote inflammation, the timing and extent of Notch activation will have to be tightly controlled. Similarly, induction of Akt in the heart might be a targeted therapy for cardiac disease. However, as with Notch, it would likely be difficult to turn on Akt in an effective and timely manner (Figure 4). In fact, it has been demonstrated that, in transgenic mice with sustained activation of Akt above a certain threshold, cardiac hypertrophy evolves into pathological remodeling with progressive functional decline. A similar phenotype has also been observed in the presence of prolonged IGF-R1 overexpression, in agreement with the development of a form of hypertrophic cardiomyopathy in human acromegaly, in which excess growth hormone causes supraphysiological increases in IGF-1 levels in the circulation and peripheral tissues, including the heart. 

Deciphering the complexity of the events regulated by Notch and Akt will be crucial for the development of new therapeutic approaches targeting these pathways individually or in synergism with others.

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Cardiac remodeling is defined by complex structural and functional modifications of the myocardium that occur after an acute myocardial injury, such as a myocardial infarction or during the development of heart failure, and cardiac remodeling is associated with poor outcomes. Increased heart rate is associated with progressive cardiac dilation and reduced ejection fraction in experimental models and in the clinic. Pharmacological heart rate reduction is generally associated with reverse cardiac remodeling; however, improvement in outcomes is variable; there is no evidence that digitalis or amiodarone improves outcomes, although they are associated with short-term reverse remodeling. In contrast, β-adrenergic blockers and the sinoatrial funny current inhibitor ivabradine induce mid-term reverse remodeling and are associated with a long-term improvement in morbidity and mortality in chronic heart failure.

Cardiac remodeling may be defined as complex genomic, molecular, cellular, and interstitial changes that result in changes in the size, shape, and function of the heart following cardiac injury or abnormal cardiac loading conditions. It occurs in various clinical conditions, including pressure/volume overload, post–myocardial infarction, myocarditis, and idiopathic dilated cardiomyopathy. Cardiac remodeling may affect the two ventricles, and also the atria, particularly in the context of prolonged/permanent atrial fibrillation. This review article will focus on the relationship between heart rate and left ventricular (LV) remodeling in heart failure.

**LEFT VENTRICULAR REMODELING AND CLINICAL OUTCOMES**

Different patterns of LV remodeling have been identified based on the measurement of LV mass index (LVMI) and relative wall thickness (RWT) in patients with heart failure and/or low ejection fraction after a myocardial infarction: concentric remodeling (ie, normal LVMI, increased RWT), eccentric hypertrophy (ie, increased LVMI, normal RWT), and concentric hypertrophy (ie, increased LVMI and increased RWT). Compared with patients without evidence of LV remodeling, patients with any of the three patterns of LV remodeling have a greater risk of cardiovascular death, myocardial infarction, heart failure, stroke, or sudden cardiac death, with the risk being the highest in patients with concentric hypertrophy. There is also a well-documented relationship between LV remodeling and long-term outcomes in patients with LV dysfunction: both LV end-diastolic and end-systolic volume or dimensions and LV ejection fraction are powerful predictors of a subsequent mortality risk in chronic heart failure or after a myocardial infarction.

Conversely, there is a relationship between the effects of heart failure drugs or devices (ie, cardiac resynchronization therapy) on ventricular remodeling and the therapeutic effects on mortality in patients with heart failure and reduced ejection fraction (HFrEF). A meta-analysis of 30 mortality trials using a total of 25 different drug/device therapies and pooling 69,766 patients, with a median follow-up of 17 months, and 88 remodeling trials performed with each of these therapies (19,921 patients followed-up for an average of 6 months) found a significant correlation between short-term effects of the drugs or devices on LV remodeling (change in ejection fraction or cardiac dimensions) and the long-term effects on mortality. This important meta-analysis suggests that LV remodeling is associated with the prognosis of the disease and that reversing LV remodeling has long-term beneficial effects, although there are some exceptions. Etanercept, a cytokine inhibitor, was shown to induce dose-dependent reverse remodeling at 3 months, but a large outcome trial with this drug failed to demonstrate any clinical benefit.
What is the role of heart rate in cardiac remodeling? - Komajda

The relationship between left ventricular remodeling and poor outcomes also exists in patients with heart failure with preserved ejection fraction (HFpEF). In a substudy of the I-PRESERVE trial (Irbesartan in heart failure with PRESERVED systolic function), 745 patients with HFpEF underwent echocardiographic determination of left ventricular volume, mass, left atrial size, and systolic and diastolic function. In this study, increased LV mass, mass/volume ratio, and left atrium size were independently associated with death or cardiovascular hospitalization and with heart failure death or hospitalization.

**LEFT VENTRICULAR REMODELING AND HEART RATE**

Experimental studies consistently show that rapid ventricular pacing induces a reduction in cardiac output, an increase in LV filling pressure, and an increase in left and right ventricular dimensions together with signs of heart failure, which occur as early as 7 days after the onset of pacing. It has been speculated that the detrimental effect of increased heart rate is linked with decreased LV filling time, imbalanced myocardial oxygen supply/demand, and abnormal ventriculoarterial coupling. In addition, impaired oxidative metabolism and enhanced oxidative stress can occur together with systolic and diastolic calcium mishandling by depletion of the adenosine triphosphate needed for myofilaments and for Ca²⁺ transport by the sarcoplasmic reticulum Ca²⁺-ATPase (SERCA). Other pathophysiological events include a reduction in sarcolemmal Na⁺K⁺-ATPase activity, increased expression of extracellular matrix proteins in the atrial tissue, and diffuse ventricular interstitial fibrosis.

In the clinical setting, studies in pace maker–dependent patients also suggest that higher pacing rates are associated with impaired cardiac function. In 15 heart failure patients, ejection fraction, assessed by gated blood pool single-photon emission tomography (SPECT), TM mode echocardiography-derived LV dimensions, Doppler parameters, and b-type natriuretic peptide (BNP) plasma concentrations, was measured in a 3-month crossover study comparing two different pacing rates (55 bpm vs 75 bpm). In the 12 patients who completed the study, high heart rate–paced patients had a significantly lower ejection fraction, higher BNP, and lower stroke volume than those paced at 55 bpm. There was also a slight and nonsignificant increase in LV dimensions, suggesting that the beneficial effect of the low pacing rate was not the result of Sterling’s law, but might be related to improved ventriculoarterial coupling through decreased arterial elastance and/or decreased myocardial oxygen consumption.

In another study randomizing two groups of pace maker–dependent patients, an increase in LV volumes and a decrease in ejection fraction was observed in patients paced at 80 bpm compared with those paced at 60 bpm. Finally, in a crossover study comparing three pacing rates (60, 75, and 90 bpm) at 2-month intervals, it was shown that the highest pacing rate (which was supraphysiological) was associated with a decrease in ejection fraction. Another piece of evidence for the detrimental role of increased heart rate on LV remodeling comes from clinical observations of tachycardia-induced cardiomyopathy, a reversible form of dilated cardiomyopathy that can result from supraventricular and ventricular arrhythmias. In a study made in children, a population devoid of cardiovascular risk factors, multivariate predictors of LV systolic functional recovery included younger age and higher presenting heart rate.

**ROLE OF HEART RATE MODULATORS**

Amiodarone and digoxin

Data on digoxin and amiodarone, two “old drugs” that reduce heart rate, are scarce. In a double-blind, placebo-controlled study, which
included 674 patients with chronic heart failure, cardiac enlargement, low ejection fraction (≤40%), and asymptomatic ventricular arrhythmias (defined by the existence of ≥10 premature ventricular contractions), high doses of amiodarone (800 mg once daily [od] for 14 days, followed by 400 mg od for 50 weeks, then 300 mg od, with a median follow-up 45 months) had no significant effect vs placebo on all-cause mortality or sudden death, although there was a nonsignificant trend for a beneficial effect in heart failure of nonischemic origin. This lack of clinical benefit was in contrast with the significant improvement in ejection fraction at 6 months.22

The more recent SCD-HeFT study (Sudden Cardiac Death in Heart Failure Trial),23 which included patients with mild or moderate heart failure, showed a lack of benefit on morbidity and mortality when adding amiodarone to conventional heart failure treatment.

In a 12-week duration study, switching from digoxin to placebo in 178 patients treated with diuretics and angiotensin-converting enzyme inhibitors resulted in worsening heart failure, decreased ejection fraction, and increased heart rate and body weight.24 However, the large outcome study DIG (DIGoxin intervention study)25 failed to demonstrate any clinical benefit for the long-term use of digoxin in patients with chronic heart failure and low ejection fraction.

It is difficult to draw any clear conclusion from these studies due to multiple limitations (eg, selection bias, absence of contemporary heart failure treatment, duration, and absence of cardiac dimension measurements). In addition, the effect of both amiodarone and digoxin is not limited to lowering heart rate, but includes other mechanisms, such as antiadrenergic effects (amiodarone), vagal stimulation, and weak inotropic effects (digoxin), that can play a role in clinical outcomes (Table 1).22-41

### Table 1. Effect of heart rate–lowering agents on cardiac remodeling and survival.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Cardiac remodeling</th>
<th>Survival</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
<td>+ ?</td>
<td>-</td>
<td>24,25</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>+ ?</td>
<td>-</td>
<td>22,23</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>+</td>
<td>+</td>
<td>28-31</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>+</td>
<td>+</td>
<td>26,30,38</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>+</td>
<td>+</td>
<td>32</td>
</tr>
<tr>
<td>Bucindolol</td>
<td>+</td>
<td>-</td>
<td>27,33</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>+</td>
<td>+</td>
<td>34-41</td>
</tr>
</tbody>
</table>

**β-Blockers**

The antiremodeling effect of β-adrenergic receptor blockers in chronic heart failure is well established. In aging male spontaneously hypertensive rats (SHR), increasing doses of metoprolol improved survival, decreased ventricular weight, prevented chamber dilation, decreased cardiac fibrosis, decreased vascular stiffness, and improved the endothelium in vascular-dependent responses, thus demonstrating both cardiac and vascular remodeling attenuation.26

Bucindolol, a nonselective β-blocking agent with mild vasodilatory properties, demonstrated a dose-dependent (12.5 mg to 200 mg) improvement in LV function, as measured by the change in ejection fraction, and a nonsignificant change, in favor of the combined bucindolol groups, resulting in a reduction in both systolic and diastolic dimensions at 12 weeks in 139 patients with chronic heart failure.27

Similar findings were reported with carvedilol, a mildly β1-selective β-blocking agent with vasodilator properties related to α1-receptor blockade, when uptitrated to 50 mg twice daily, in a group of 60 heart failure patients with a low ejection fraction. After 3 months of administration, a marked improvement in ejection fraction and LV stroke work was observed.28

A small sub study of the MERIT-HF trial (MEtoprolol MR/XL Randomized Intervention Trial in congestive Heart Failure) showed similar results in 41 patients with chronic heart failure treated with metoprolol, a β1-selective β-blocking agent. A decrease in LV end-diastolic and end-systolic volume index, measured by cardiac magnetic resonance, was observed, whereas the ejection fraction increased significantly.29

Larger and/or longer studies have confirmed the beneficial effect of β-blockers on remodeling. In the RESOLVD trial (Randomized Evaluation of Strategies For Left Ventricular Dysfunction), metoprolol, administered for 24 weeks, was associated with an increase in ejection fraction and an attenuation in the increase in LV end-diastolic and end-systolic values.30

In a group of 48 elderly patients with New York Heart Association (NYHA) class III and an EF <35%, carvedilol significantly improved diastolic and systolic diameters, LV mass, systolic volume, and ejection
fraction, measured by echocardiography, compared with placebo after 12 months of treatment. Interestingly, only LV end-diastolic diameter was significantly reduced in the carvedilol group at the 3-month evaluation.

In a subgroup of 160 patients from the CIBIS study (Cardiac Insufficiency Bisoprolol Study), LV end-systolic diameter significantly decreased and fractional shortening significantly increased in the bisoprolol-treated patients compared with placebo after 5 months of treatment. Change in fractional shortening was not significantly correlated with bisoprolol-induced heart rate reduction, but was associated with improved outcomes.

Finally, the BEST trial (Beta-Blocker Evaluation of Survival Trial) evaluated the impact of bucindolol in a population of 2708 patients with NYHA class III and IV heart failure. The trial failed to demonstrate any benefit on survival, although there was a significant improvement in LV ejection fraction at 3 and 12 months. The absence of a distinct association observed between survival and reverse remodeling in the BEST trial is not clearly understood. However, it points to the complexity of the relationship between heart rate change, remodeling change, and β-blocker therapy. Indeed, the CIBIS substudy showed that heart rate reduction, change in LV fractional shortening, and bisoprolol treatment independently contributed to the improvement in survival.

In addition, other factors, such as β1-cardioselectivity, vasodilatory properties, magnitude of the heart rate reduction, and heart rate unrelated mechanisms of action, can play a significant role in the relationship between reverse remodeling and survival observed with β-blockers in chronic heart failure (Table I).

### Ivabradine

The recently developed funny (f) channel blocker ivabradine has been extensively studied in chronic heart failure. In rats with heart failure induced by coronary artery ligation, a 90-day treatment with ivabradine decreased heart rate, reduced LV end-systolic, but not end-diastolic, diameter, and increased stroke volume. There was also a shift to the left of the LV pressure-volume relation, a decrease in LV collagen density, and an increase in LV capillary density, suggesting that ivabradine treatment induced a favorable structural change in the myocardium and interstitial tissue. Several mechanisms have been hypothesized to explain the myocardial structural change induced by ivabradine in experimental chronic heart failure, including myocardial angiogenesis, enhanced coronary perfusion time, improvement in the O2 supply/demand ratio, and prevention of endothelial dysfunction, local hypoxia, and local production of cytokines and free radicals.

The beneficial effect of ivabradine on LV electrophysiological and structural remodeling and energy consumption of the myocardium was confirmed in another study using a similar experimental model. In addition, a significant correlation was found between heart rate and cardiac energy metabolism in this study.

In a diabetic mouse model of heart failure with preserved ejection fraction, heart rate reduction by ivabradine for 4 weeks improved LV end-systolic elastance, contractility, and diastolic function. In addition, ivabradine prevented changes in the expression of the “stiff” N2B isoform of titin and phosphorylation of phospholamban.

In a mouse model of angiotensin II-induced heart failure, ivabradine, administered for 3 weeks, led to a significant improvement in systolic and diastolic LV function and less cardiac hypertrophy, fibrosis, inflammation, and cardiac apoptosis, whereas metoprolol, administered at a dose leading to a similar heart rate reduction, did not prevent the adverse remodeling. This finding suggests that prevention of adverse remodeling after chronic stimulation of the renin-angiotensin-aldosterone system was achieved better by β1 blockade than by β-adrenergic blockade. Similar findings have been observed in a rat model of heart failure following coronary ligation and mechanical unloading, which was induced by heterotopic abdominal heart transplantation, after 4 weeks of ivabradine infusion compared with metoprolol. Ivabradine, but not metoprolol, reversed myocardial fibrosis both alone and in combination with mechanical unloading. In addition, ivabradine alone enhanced the restoration of abnormal excitation contraction coupling.

In 6900 patients with chronic heart failure, low ejection fraction (≤35%), increased heart rate (≥70 bpm), in sinus rhythm, and treated with contemporary heart failure medications, including β-blockers in 90% of cases, ivabradine significantly improved the primary outcome of cardiovascular mortality or heart failure hospitalization compared with placebo. The benefit of ivabradine was directly related to the magnitude of heart rate reduction achieved by the drug and the absolute heart rate achieved. An echocardiographic substudy, conducted in 411 patients, demonstrat-
ed that treatment with ivabradine significantly reduced LV end-systolic and end-diastolic volume index and improved ejection fraction at 8 months. The improvement in LV end-systolic volume index was independent of β-blocker use, suggesting that I$_f$ channel blockade reverses cardiac remodeling. In addition, the study further supports the role of heart rate in cardiac remodeling. Compared with those with lower heart rates, patients with a heart rate ≥77 bpm at baseline had a larger LV end-systolic volume index and lower ejection fraction at baseline. Furthermore, an inverse relationship between the change in heart rate and the change in LV ejection fraction was observed.

The potential mechanism for the beneficial effect of ivabradine on cardiac remodeling could result from a heart rate–dependent improvement in total arterial compliance, effective arterial elastance, and therefore, ventriculoarterial coupling via unloading of the left ventricle. This was suggested in an echocardiographic substudy of the SHIFT trial (Systolic Heart failure treatment with the I$_f$ inhibitor ivabradine Trial), where both arterial elastance and total arterial compliance were measured at baseline and after 8 months of treatment in 275 patients.

The effect of I$_f$ channel blockade on cardiac remodeling was further confirmed by an echocardiographic substudy of the BEAUTIFUL trial (morBidity-mortality EVAlUaTion of the I$_f$ inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction), which was performed in 426 patients from the morbidity and mortality evaluation of ivabradine in patients with coronary disease and left ventricular dysfunction. Treatment with ivabradine was associated with a decrease in LV end-systolic volume index and an increase in ejection fraction vs placebo. Reduction in LV end-systolic volume index was related to the degree of heart rate reduction with ivabradine (Table I).

**CONCLUSION**

Cardiac remodeling is central to the development of clinical heart failure and is a powerful predictor of cardiovascular events in patients with reduced ejection fraction. The relation between cardiac remodeling and heart rate is suggested by both experimental and clinical studies. Increased heart rate is associated with a number of functional cardiovascular abnormalities, including impaired oxygen supply/demand ratio and abnormal ventriculoarterial coupling, which can induce structural abnormalities leading to cardiac remodeling.

Reversal of cardiac remodeling by heart rate reduction has been observed with several heart rate–lowering agents, but benefits on clinical outcomes have only been demonstrated for β-blockers and ivabradine.

Whether the clinical benefit observed with these two classes of heart rate–reducing agents is solely dependent on heart rate reduction remains unclear and deserves further mechanistic studies.

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Ventricular remodeling: the appropriate surrogate end point for cell-based therapy?

Shahab Ghafghazi, MD; Marcin Wysoczynski, PhD; Matthew C. L. Keith, MD; Joseph B. Moore IV, PhD; Roberto Bolli, MD

Division of Cardiovascular Medicine - Department of Medicine - University of Louisville - Louisville - KY - USA

Prevention and reversal of left ventricular (LV) remodeling in ischemic cardiomyopathy are important therapeutic goals because LV remodeling is directly associated with adverse clinical outcomes. Although imaging parameters of remodeling are surrogate markers for clinical outcomes, the optimal surrogate end points in stem cell trials remain unknown. Meta-analyses show a modest beneficial effect on ejection fraction and LV remodeling when using stem cells. Conclusive evidence for cell-based therapies on LV function and structure requires large phase 3 trials. Here, we will review the literature on the significance of LV remodeling relating to clinical end points and remodeling indices as surrogate outcomes in trial design, and summarize the most important clinical trials on cell-based therapy.

Cardiac regeneration was in the realm of science fiction until the beginning of the millennium. For most of the 20th century, the mammalian heart was considered a postmitotic organ, hence incapable of regeneration. The regenerative cardiology revolution was heralded by the description of cardiac repair by skeletal myoblasts and bone marrow cells (BMCS) in preclinical models. These reports provoked intense interest, and within a short period, were followed by phase 1 clinical trials in patients with acute myocardial infarction (AMI). Over the past 15 years, a flurry of progenitor/stem cells have been tested for their potential to regenerate dead/scarred myocardium in the context of AMI and chronic cardiomyopathy (Figure 1); these include skeletal myoblasts, bone marrow mononuclear cells (BMNCs), mesenchymal stromal cells (MSCs), proangiogenic progenitor cells, and cardiac progenitor cells (CPCs).

The term “left ventricular (LV) remodeling” describes the LV structural alterations in response to long-standing changes in loading conditions. Three patterns of remodeling exist: (i) concentric remodeling secondary to pressure overload; (ii) eccentric remodeling secondary to volume overload; and (iii) remodeling after MI, a complex amalgamation of the other two patterns. Since stem/progenitor cells have been predominantly studied in ST-segment elevation MI (STEMI) and ischemic cardiomyopathy (ICM), we will review the effect of cell therapy on ventricular remodeling in these two settings.

LEFT VENTRICULAR REMODELING

If left unchecked, eccentric remodeling is progressive and results in unabated LV dilation and dysfunction. Eventually, the common phenotype of a dilated spherical heart ensues, irrespective of the nature of the original insult. The pathology includes hypertrophy of surviving cardiomyocytes, interstitial fibrosis, apoptosis, and autophagy, among other derangements.

Furthermore, profound neurohumoral perturbations occur. Although LV enlargement is initially adaptive to maintain cardiac output, it eventually becomes maladaptive, leading to further LV dilation and contractile dysfunction. Current evidence-based treatments include renin-angiotensin-aldosterone system inhibition, β-adrenergic receptor blockade, and cardiac resynchronization therapy. These approaches can retard the progression of the disease; nevertheless, a sizeable number of patients develop end-stage heart failure. The limited capacity for renewal of the heart is overwhelmed by the initial insult and subsequent remodeling process.
LV remodeling is traditionally gauged by measurements of LV volume, including LV end-systolic volume/diameter (LVESV/LVESD), LV end-diastolic volume/diameter (LVEDV/LVEDD), their indices (the volume/diameter divided by body surface area), LV mass, and segmental wall thickness. Although LV ejection fraction (LVEF) is not a direct remodeling index, it is influenced by the remodeling process more than any other factor.15 Echocardiography is the most common method for assessing remodeling and tremendous advances have been made in terms of reliability and reproducibility.22,23 Nonetheless, cardiac magnetic resonance imaging (CMRI) is the most accurate method for anatomical and functional LV assessment.24 It is a three-dimensional (3D) technique, which is free of geometric assumptions in volumetric calculations,25 and is widely accepted as the “gold standard” in view of its unmatched resolution and excellent reproducibility.25,26 The latter characteristic could translate into a substantial reduction, as much as 80%, in the sample size required to detect a statistically significant outcome in clinical trials.27 Moreover, with the use of gadolinium, scar size/mass and microvascular obstruction can be measured, both of which are associated with remodeling.15 An additional technique is 3D echocardiography, which has been shown to be superior to B-mode echocardiography in terms of reproducibility and is highly correlated with CMRI.28-32 Segmental function is another important parameter for LV remodeling. Traditionally, it is quantified by measuring the average wall thickening within each ventricular segment. A more advanced method of measurement is by strain analysis, using either echocardiography or tagged CMRI.33 Finally, regional EF is an invaluable remodeling parameter that provides information on the function of adjacent myocardial segments.

**IMPORTANCE OF VENTRICULAR REMODELING**

LVEF is one of the best surrogate outcomes in cardiovascular medicine.26,34-36 Below 45%, every 10% reduction in LVEF is associated with a 39% increase in the risk of all-cause mortality.37 In addition, a large body of evidence in patients with AMI, cardiomyopathy, and even in patients free of overt cardiovascular disease, demonstrates that various indices of LV remodeling correlate with “hard” end points.36 These indices could be even more predictive of survival than LVEF. White et al demonstrated that patients with AMI, LVESV, and LVEDV had higher predictive values for survival than
In a subgroup of patients in the GUSTO-I study (Global Utilization of STreptokinase and t-PA for Occluded coronary arteries), Migrino et al found that the LVESV index, administered soon after reperfusion therapy for AMI, strongly predicted adverse outcomes, including mortality. Finally, in a group of patients with advanced heart failure, the LVEDV index was predictive of survival, independent of LVEF. Longitudinal changes in remodeling are also prognostically important. In the Val-HeFT trial (Valsartan Heart Failure Trial), both the baseline LVEDD index and its change over time were associated with outcomes independently of LVEF.

Other parameters of remodeling, such as scar size/mass (measured by late gadolinium enhancement and microvascular obstruction), can also constitute important prognosticators. The fact that these parameters can be measured solely with CMRI highlights the increasingly prominent role of CMRI in the cardiac regeneration field. In a study of STEMI patients, the number of LV segments with transmural infarction (defined by a late gadolinium enhancement ≥75% of the segmental thickness) was predictive of subsequent LV remodeling. Additionally, the extent of late gadolinium enhancement predicts the likelihood for functional recovery after coronary revascularization or medical therapy. In another study, myocardial segments with microvascular obstruction early post-STEMI showed late wall thinning and no functional recovery at 5 months. In addition, severe microvascular obstruction is correlated directly with remodeling and inversely with LV function at 6 months. Finally, quantification of myocardial strain is predictive of clinical outcomes. In a prospective cohort of 546 patients followed for an average of 5.2 years, global longi-
Ventricular remodeling: the appropriate surrogate end point for cell-based therapy? - Ghazghazi and others

The use of LVEF as the surrogate outcome of choice for clinical end points offers multiple benefits, including a strong correlation with clinical end points, simplicity of a single, yet powerful, index, ease of measurement, and familiarity of practicing physicians. However, there are also drawbacks. For example, in the CHARM study (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity), LVEF had no differential predictive value for clinical outcomes at levels above 45%. This may be partly due to subtle abnormalities of segmental LV function that are not amenable to quantification with a global end point like LVEF. Another explanation is that even overt regional wall motion abnormalities may not lower global LVEF to levels <45% when the unaffected regions of the left ventricle exhibit compensatory hyperkinesis. Interestingly, many earlier cell therapy trials enrolled patients with an LVEF ≥45%, most of these trials failed to observe an improvement in LVEF with cell therapy, in contrast to trials that enrolled only patients with an LVEF <45%. In view of these facts, if LVEF is used as an end point, studies of cell therapy should probably be limited to patients with LVEF <45%. Subtle changes in LVEF (1% to 5%) should not be dismissed as clinically insignificant, in fact, such small changes may translate into meaningful clinical outcomes, as seen with evidence-based therapies like β-blockers.

Parameters of LV remodeling are diverse and reflect different aspects of its pathophysiology. While some (LV volume) are global in nature, others (strain) are regional. Some (wall thickening) assess diseased and healthy segments alike, while others (late gadolinium enhancement) solely measure injured segments. Subtle structural changes due to the remodeling process could potentially be measured more efficiently by parameters, such as strain analysis, due to their segmental nature. Since cell therapy, whether by endomyocardial or intracoronary administration, is often delivered to diseased segments, it is desirable to differentially evaluate the effects of treatment on receiving, adjacent, and remote segments. Accordingly, remodeling parameters may impart superior prognostic discrimination for clinical outcomes in comparison with the global LVEF.

Yet, the strength of the remodeling parameters also constitutes their weakness. If the parameters do not change in unison, appropriate interpretation of discrepant indices may be challenging. One solution is to incorporate these parameters into a single composite end point that reflects both regional and global parameters. Based on these considerations, the National Heart, Lung, and Blood Institute (NHLBI)-sponsored Cardiovascular Cell Therapy Research Network (CCTRN), which was established to conduct early multicenter phase (phase 1 or 2) trials on cell therapy, has incorporated regional function and remodeling indices in their primary end points. It should be noted that the use of CMRI enables a simultaneous evaluation of both global and regional parameters, comparative analyses among them, and even exploration of new composite indices or computational models. By facilitating a differential examination of the effect of therapy on segmental and regional function, this approach promotes mechanistic explorations. The data published to date by the CCTRN show a concordance between global LVEF and regional parameters, albeit in largely negative studies. At present, it is unclear which parameters of LV function or remodeling correlate best with hard clinical outcomes. Hopefully, this question will be answered by larger trials powered to detect changes in morbidity and/or mortality. Until these questions are elucidated, it seems prudent to recommend that clinical trials on cell-based therapies use, as end points, multiple parameters of LV remodeling (eg, LVEF, regional wall motion, scar size, LVESV), rather than relying on just one (eg, LVEF).

In the following section, we will briefly review the effect of various stem/progenitor cells on LV remodeling in the clinical trials conducted so far.

Skeletal myoblasts

Skeletal myoblasts were the first cells tested for cardiac regeneration. The MAGIC trial (Myoblast Autologous Grafting in Ischemic Cardiomyopathy), the largest study investigating the efficacy of skeletal myoblasts in patients with ICM (LVEF <35%), randomized 97 patients...
to low- or high-dose cell therapy or to placebo during coronary artery bypass graft surgery (CABG). The study failed to show any improvement in LV function in treated patients. Administration of skeletal myoblasts has been plagued by an increased incidence of ventricular arrhythmias; furthermore, many of these trials, including MAGIC, were performed along with CABG, complicating the interpretation of the results. Due to these factors, interest in skeletal myoblasts has almost vanished.

**BONE MARROW–DERIVED STEM/PROMINENT CELLS**

Bone marrow–derived progenitor cells have been used more than any other cell type in clinical trials of cardiac repair, this is due to the relatively high density of stem cells in the bone marrow and the ease of procurement. Bone marrow contains various stem cell populations, including hematopoietic stem cells, endothelial progenitor cells, and MSCs. Bone marrow stem cells have either been used as an unfractonated population, ie, bone marrow mononuclear cells (BMMNCs) or specific populations, including MSCs and CD34+ cells, that have been isolated and administered. In this section, we will review the effect of these cells on ventricular remodeling.

**Bone marrow mononuclear cells**

**Acute myocardial infarction**

BMMNCs are especially attractive in STEMI patients because they do not need to be cultured and can be delivered shortly after an AMI. A large number of clinical trials have been performed in the setting of both AMI and cardiomyopathy.

In the BOOST trial (Bone marROW transfer to enhance ST-elevation infarct regeneration), 60 patients with STEMI were randomized to receive BMCs or placebo. At 6 months, the treated group exhibited a statistically significant improvement in global and regional EF and wall motion in the border zone, but not in LV volume. Despite this early benefit, the improvement was no longer present at 18 months, mainly because there was an improvement in the control group.

The largest study to date was REPAIR-AMI (Reinfusion of Enriched Progenitor cells And Infarct Remodelling in Acute Myocardial Infarction), a double-blind, randomized clinical trial (RCT) that assigned 204 patients with STEMI to an intracoronary infusion of BMMNCs or placebo soon after a successful reperfusion. Compared with placebo, in the bone marrow group, there was a statistically significant improvement in LVEF at 4 months and in a number of combined clinical end points including death and recurrent MI at 1 year. There was also a concordant reduction in LV volume, although it did not reach statistical significance. At 2 years, all of the composite end points remained significantly improved, at the 5-year follow-up, the composite of death, recurrent MI, and any revascularization was statistically different between the cell-treated group and the placebo group, which was driven mainly by revascularization. Further analysis suggested that BMC therapy, but not placebo, abrogates adverse remodeling, as demonstrated by smaller end-diastolic wall thickness in the treated and remote areas along with enhanced regional contractility.

In contrast to REPAIR-AMI, two other simultaneous studies reported no benefit from BMMNCs in AMI. In the ASTAMI trial (Autologous Stem cell Transplantation in Acute Myocardial Infarction), 100 patients with STEMI were assigned to BMMNCs or control in an open-label RCT. The two groups did not differ with respect to LVEF, LVEDV, or infarct size at 6 months. Janssens et al randomized 67 patients with STEMI to BMMNCs vs placebo. At 4 months, there was no improvement in LVEF although infarct size and regional LV function improved in the therapy group.

More recently, four contemporaneous phase 2 RCTs have tested BMMNCs in AMI. In the HEBE trial (evaluation of the effects of intracoronary infusion of autologous BMMNCs and the effects of intracoronary infusion of autologous PBMCs after primary percutaneous coronary intervention), a multicenter open-label RCT, 200 patients with AMI and successful reperfusion were assigned to intracoronary BMMNCs, mononuclear peripheral blood cells, or standard therapy. There were no differences between the groups in terms of LVEF, LV volume, LV mass, infarct size, or in clinical events.

In the CCTRN TIME trial (Timing In Myocardial Infarction Evaluation), 120 patients with STEMI, LVEF ≤45%, and successful reperfusion were randomized 2:1 to early intracoronary BMMNCs or placebo. At 6 months, the treatment had no significant effect on recovery of global or regional LV function or LV volume compared with placebo. In the CCTRN LateTIME study, which was designed to investigate the benefit of BMMNCs administered 2 to 3 weeks after AMI, 87 patients with LVEF ≤45% following STEMI were randomized 2:1 to intracoronary BMMNCs or placebo. Again, the treatment did not improve LV function (global or regional) or LV volume at 6 months. Finally, in the SWISS-AMI trial (SWISS multicenter intracoronary stem cells study in Acute Myocardial Infarction), 200 patients with successfully reperfused
STEMI were randomized 1:1:1 to an open-labeled control or two intra-coronary BMMNC treatment groups (early [5 to 7 days] and late [3 to 4 weeks] administration) 67 Again, there was no improvement in LVEF, scar mass, or LV volume at 4 months. Of note, in the above trials, all measurements were done with CMRI.

Multiple reasons have been proposed for the inconsistent results observed in BMMNC trials, including heterogeneous infusate and progenitor content (eg, percent of CD34+ and CD133+ cells),68 methodological differences in bone marrow processing,69-71 and timing of administration of cells, although the latter has been addressed in recent studies.52,53,67 It is becoming evident that the specific bone marrow processing protocol plays a major role in the viability and properties of the cells that are injected into the patients. Multiple meta-analyses of bone marrow trials in AMI have demonstrated statistically significant, albeit modest, improvements in LVEF (~2% to 3%), LV volume, scar mass, and some clinical outcomes, such as recurrent MI.57,72,73 However, the benefits disappear when the analysis is limited to studies that used CMRI for outcome assessment.51,72,74 Additionally, the more recent and methodologically robust studies have all been negative.52,53

Ischemic heart failure
BMMNCs have also been utilized in the treatment of chronic ischemic cardiomyopathy. After positive pilot trials,1 FOCUS-CCTRN (First mOnonuclear Cells injected in the United States conducted by the CCTRN) randomized 154 patients with ICM, LVEF ≤45%, and NYHA classes II and III to endomyocardial injection of BMMNCs or placebo.54 There were no differences between the two groups for LV remodeling, global and regional end points, or clinical outcomes. The results of meta-analyses suggest that cell therapy produces a modest improvement in LVEF, LV volume, and clinical outcomes.75,76 In summary, there is no significant heterogeneity between LVEF as the end point of choice, the parameters of LV remodeling, and regional EF in the larger trials done heretofore. A more definitive answer regarding the efficacy of BMMNCs is expected from the open-label BAMI trial (effect of intracoronary reinfusion of Bone marrow-derived mononuclear cells on all-cause mortality in Acute Myocardial Infarction).77 which plans to randomize 3000 STEMI patients with an LVEF ≤45% to BMMNC or control, with mortality as the primary end point.

Proangiogenic progenitor cells
This category includes CD34+ and CD133+ cells, both of which are present among the BMMNCs in small proportions (~1% to 2%).53,78 These cells are sorted out of the BMMNCs by immunomagnetic selection. In the open-label REGENT RCT (myocardial REGENeration by intracoronary infusion of a selected population of stem cells in acute myocardial infarction), a head-to-head comparison was performed among BMMNCs, CD34+/CXCR4+ BMCS, and control (no treatment) in patients with LVEF <40% post-MI.79 Overall, there were no significant differences between groups regarding LVEF, LV volume, and clinical end points at 6 months as assessed by CMRI. Vrtovacek et al randomized 110 patients with non-ischemic cardiomyopathy to intracoronary CD34+ cells vs control (no treatment) in an open-label study.80 At 1 year and 5 years, treated patients exhibited improved LVEF by echocardiography and decreased mortality. There was, however, no difference in LVEDD between the groups. Finally, in the Cardio133 trial (Coronary artery bypass graft surgery and CD133 marrow cell injection for treatment of ischemic heart failure), 60 patients with ICM (LVEF <35%) were randomized to undergo both CABG and intramyocardial injection of CD133+ cells in the hypokinetic infarct border zone or CABG and a placebo injection.81 At 6 months, using CMRI, cell therapy had no effect on LV function and volume or clinical symptoms. With the exception of the Vrtovacek study in nonischemic cardiomyopathy, the studies done to date do not indicate a different therapeutic efficacy of the selected BMCs in comparison with unselected BMMNCs.

Mesenchymal stromal cells
MSCs have become the focus of increasing attention in recent years because of their in vitro stemness characteristics, ease of isolation and expansion, and favorable immunomodulatory profile68,82, the latter property means that they have the ability to evade or suppress the immune system to the extent that they can be used in an allogeneic fashion with no requirement for concomitant immunosuppression.82 This property facilitates “off-the-shelf” use, first and foremost for AMI, but also for cardiomyopathy. In the latter case, an “off-the-shelf” product eliminates protracted waiting time for expanding autologous cells and makes the cell therapy readily available, similar to BMMNCs. Additionally, the ability to procure the cells from a young healthy donor using an allogeneic transplant may translate into more efficacious cell products. MSCs have been used in the setting of AMI. Hare et al performed a head-to-head comparison of intravenous allogeneic MSCs and placebo in 53 patients with STEMI after...
Markers.

in the inevitable use of surrogate underscores the challenges inherent c-kit + CPCs. The fact that these Ischemic cardiomyopathy) with Ventricular remodeling: the appropriate surrogate end point for cell-based therapy? - Dialogues in Cardiovascular Medicine - Vol 20 . No. 2 · 2015

segments. This phenomenon has lowest effect in remote untreated (Stem Cell Infusion in Patients with beneficial actions occurred despite fashion, with the greatest benefit LV sphericity index (markers of ventricular remodeling), although there was no improvement in LVEF. Further analysis suggested that scar size reduction was evident in all scarred segments, whether or not they were treated, although the magnitude of reduction was greater in treated segments; conversely, segmental EF improved only in the scarred segments that received treatment. Furthermore, the greatest improvement in segmental EF was observed in the injected scarred segments with an EF  20%. The improvement occurred in a centripetal fashion, with the greatest benefit in the cell-treated areas and the lowest effect in remote untreated segments. This phenomenon has also been seen in the SCIPIO trial (Stem Cell Infusion in Patients with Ischemic cardiomyopathy) with c-kit+ CPCs. The fact that these beneficial actions occurred despite no improvement in LVEF further underscores the challenges inherent in the inevitable use of surrogate markers.

In the TAC-HFT trial (Transendocardial Autologous mesenchymal stem Cells and mononuclear bone marrow cells in ischemic Heart Failure Trial), 65 patients with ICM and an LVEF <50% were randomized to MSCs, BMMNCs, or placebo. At 1 year, infarct size was reduced in the MSC group, but not in the BMMNC or placebo groups. Moreover, regional myocardial function at the site of injection, quantified by circumferential strain, improved with MSCs, but not with BMMNCs or placebo. Nonetheless, there were no differences in LVEF and LV volume among the groups. Finally, in the C-Cure trial (Cardiopoietic stem Cell therapy in heart failure), 47 patients with ICM (LVEF <40%) were randomized to “cardiopoietic” MSCs (pretreated with a cardiospecific cocktail) or control. At 2 years, LVEF and LVESV significantly improved with cell therapy vs control. A more definitive assessment of the therapeutic potential of MSCs will likely come from an ongoing phase 3 trial (Efficacy and safety study of allogeneic mesenchymal precursor cells [CEP-41750] in patients with chronic heart failure due to left ventricular systolic dysfunction of either ischemic or non-ischemic etiology) that is randomizing 1730 patients with ischemic or nonischemic cardiomyopathy to MSCs or placebo. The bone marrow encompasses other progenitor cells, such as the aldehyde dehydogenase–bright stem cells that were recently tested in a small proof-of-concept study. MSCs can also be isolated from sources other than bone marrow, eg, adipose tissue.

CARDIAC-DERIVED PROGENITOR CELLS

In 2003, Beltrami et al described resident CPCs in the adult mammalian heart. These cells expressed c-kit, a tyrosine kinase receptor, and an established stem cell marker. Injected into a rat model of myocardial infarction, the cells improved cardiac function and reduced infarct size. Subsequently, the presence of CPCs in human myocardium was demonstrated.

After extensive preclinical work, Bolli et al embarked on the first clinical trial of c-kit+ CPCs. Approximately 4 months after CABG, 1 million autologous CPCs, isolated and expanded from the right atrial appendage harvested during CABG, were administered intracoronarily to 20 patients with ICM. 13 patients, who received no treatment, were enrolled as controls. At the 1-year interim analysis, CPC administration was associated with an impressive 12.3% improvement in LVEF and a parallel improvement in regional function in the infarcted regions infused with CPCs (Figure 2). In contrast, no significant changes were noted in the control group. Additionally, CMRI assessment of treated patients suggested a reduction in scar burden accompanied by an increase in LV viable myocardium.

Notably, the salubrious effect of CPCs was more pronounced in the LV segments with the greatest amount of transmural infarct and contractile dysfunction; in other words, the lower the baseline function in a segment, the greater the functional recovery afforded by CPCs.

In the CADUCEUS trial (Cardiosphere-Derived autologous stem CELls to reverse ventricular dySfunction), 25 patients with ICM were randomized to receive intracoronary cardiosphere-derived cells (CDCs) or control (standard care). CDCs are a heterogeneous mixture of different cell types, including stem/progenitor cells (eg, MSCs, c-kit+...
CPCs). Although there was no statistically significant improvement in LVEF in the treated group, a reduction in scar mass, an increase in viable mass, and an improvement in regional contractility were reported at 6 and 12 months by CMRI. No improvement was detected in the control group.

Importantly, there is emerging evidence that cardiac-derived cells are tissue committed MSCs. Accordingly, they may be immune privileged, similar to bone marrow–MSCs. This would be an important advantage in cell therapy, as detailed above. Allogeneic CDCs are already being tested in the ongoing ALLSTAR trial (ALLogeneic heart Stem cells to Achieve myocardial Regeneration)93 in patients with ICM.

**FUTURE DIRECTIONS**

In just a little over a decade, an enormous amount of basic, preclinical, and clinical investigations related to cell therapy have been performed, including more than 100 clinical trials. In fact, for BMMNCs and MSCs, there are ongoing phase 3 RCTs. Nevertheless, many important questions remain unanswered. For example, the mechanism of the observed benefits is unclear, since functional benefits occur despite poor cell retention in vivo due to a paucity of homing and/or survival of the administered cells (Figure 3, page 134). There are also unanswered translational questions, such as the most efficacious cell type, the best dose or range of doses, the appropriate time of therapy in the case of AMI, single- vs combined-cell therapy, single vs repeated administration of cells, and last, but
not least, the most appropriate route of administration. Future studies should be designed to address such questions. A considerable amount of research is also focusing on tissue engineering, which may resolve some of the aforementioned questions and will likely be an integral part of successful cell therapy in the future.

CONCLUSIONS

LV remodeling is an undesirable and frequently progressive consequence of AMI and chronic cardiomyopathy, and it is associated with adverse clinical outcomes. Current treatments are essentially palliative. It is of the utmost importance to develop new modes of therapy to halt this process and even restore, at least in part, lost myocardium. Stem/progenitor cell therapy has the potential to meet this need. There is considerable evidence to suggest that parameters of LV remodeling are as good a surrogate marker of clinical improvement as LVEF, if not better. Although the majority of the trials performed to date show a concordance between LVEF and remodeling, the optimal surrogate end points in therapies aimed at LV remodeling remain unknown. The use of CMRI in stem cell trials is particularly advantageous because it allows simultaneous measurement of multiple end points, including global and regional EF and indices of LV remodeling. The collective evidence gathered thus far suggests that cell therapy confers a modest beneficial effect on LVEF and is associated with reverse LV remodeling and even favorable clinical outcomes. Ongoing phase 3 trials will provide a definitive answer regarding the true therapeutic value of stem/progenitor cells.

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WHY DO WE ENJOY ART?

When did our ancestors start drawing pictures? Art harks back to the very origin of mankind—arguably, it is what made humans human. The oldest known paintings—six paintings in red ochre depicting seals—in the Caves of Nerja in the province of Málaga in Spain, are thought to be over 42 000 years old. For José Luis Sanchidrián of the University of Cordoba in Spain, such antiquity suggests that these marine animals were more likely to have been painted by Neanderthals (Homo neanderthalensis) than by early modern humans (Homo sapiens).

According to some paleoanthropologists, the same is also true of the stenciled handprints and red disks produced by blowing pigments onto the cave wall in another cave in Spain, the El Castillo cave, in the province of Cantabria. Many questions remain unanswered, such as regarding possible contacts between Homo sapiens and Neanderthals. But the fact that Neanderthals engaged in some form of art implies that they were “the mental equals of modern humans,” as is being increasingly postulated in scientific papers (see the fascinating paper by Appenzeller T. Neanderthal culture: old masters. Nature. 2013;497:302-304). But the two really crucial questions are: what drove our ancestors to paint the walls of caves, and to which extent did they experienced their paintings as art?

These two questions still nag us today. What does one feel and what does one think when looking at a painting, what makes one find a painting beautiful or be untouched by it? And, what drives a painter to paint? These are highly subjective matters, and probably ultimately idle questions. However, most people probably experience delight and happiness when looking at a beautiful painting, or when painting, if they are a painter. And that is certainly my experience both as a viewer and as an artist.
ARCHITECTURE AND MEDICINE

From a very early age, I developed a keen interest in Greek and Roman architecture and European classical culture, including music and paintings. At the time, South Korea was trying to cope with the economic consequences of the 1950-1953 War and was dependent on US aid. Nonetheless, I was able to carry on my studies and look forward to the future. In high-school, I longed to become an architect, but then changed my mind and matriculated at medical school to become a physician. Eventually, I specialized in cell pathology and cardiology. After graduation, I worked in a lab where I used a transmission electron microscope to study gestation-associated changes in the human fetal heart and cardiac ischemia-reperfusion injury in
animals. However, most of this work was routine, and I had the feeling that I wasn’t really getting anywhere. But then, at the XXth European Congress of Cardiology, Vienna, Austria, in 1988, I had the good fortune of meeting Professor Wolfgang Schaper, head of the Department of Experimental Cardiology at the Max-Planck Institute in Germany. Thanks to him, my entire outlook on science and research changed, and I had the opportunity to be part of state-of-the-art cardiovascular research at the Max Planck Institute under his aegis. I returned as a seasoned researcher to South Korea, at the Sungkyunkwan University School of Medicine, in Suwon, first in the Department of Anatomy and Cell Biology, and later in the Department of Anatomy Cardiovascular Research Unit. I currently work as a volunteer for a group whose purpose is to develop a reliable tool for the early diagnosis of small atherosclerotic lesions. And I still paint pictures for my work and for my daily life.

**EUROPE ON MY EASEL**

For more than 40 years now I have enjoyed painting townscapes, still lifes, or portraits. I visited Europe for the first time in 1983, on the occasion of a scientific meeting, and the ancient buildings, castles, palaces, and theaters were a revelation, as were the museums. I was especially drawn to the paintings of the Impressionists and Paul Cézanne. After that encounter with European architecture and art, I took to always carrying a sketchbook with me to draw churches, castles, palaces, and other ancient buildings when travelling abroad for scientific meetings or for leisure. Among my list of favorite places in Europe: Montmartre in Paris; the Lyon botanical garden; the Nymphenburg palace in Munich; the Städl Museum in Frankfurt; the Heidelberg Castle; the Rothenburg Castle; the Würzburg Residence; Salzburg, with the Festung (Castle) on a hill overlooking the Old City and its many baroque churches (Cathedral, Franciscan Church, St Peter’s Church) and the Getreidegasse with its hanging wrought-iron shop signs; the Hofburg Castle in Vienna; the city of Graz; The Castle (Prazsky Hrad) and Golden Lane (Zlatá ulička) in Prague; the Buda Castle in Budapest; the Thames and Tower Bridge in London; the Old Town (Gamla Stan) in Stockholm; the Roman ruins in Rome; San Marco in Venice; the Ponte Vecchio in Florence; the Cathedral of Milan; the Seine in Paris in autumn. Oil on canvas.
medieval buildings of Bologna; the Parthenon of Athens; the white and blue houses of Santorini; etc. etc. I’ll never cease to draw or paint!

**A CONFUCIAN UPBRINGING AND APPRECIATION OF ART**

I grew up in a Confucian family. Confucianism tends to be equated with strict personal ethics and respect of social stratification, but my parents were quite liberal in certain aspects. Also, it should never be forgotten that for Confucius the arts played an absolutely central role and that, according to his teachings, the ‘gentleman’ needs to excel in the arts, in particular music, poetry, calligraphy/painting (the latter two were for the ancient Chinese, and Koreans, a one and same form of art).

Does this explain why, alongside painting, I also developed a passion for classical music? Classical music and painting are as essential for me in my daily life as they are in my practice of cardiology. I sometimes liven up my lectures with my own paintings or those of others, as well as classical music, as the late Peter Harris used to do (see article by Ruigrok TJC, Anand IS, Ferrari R. Art and the Heart. Peter Harris, the scientist, the clinician, and the artist—the Complete Man. *Dialogues in Cardiovascular Medicine.* 2012,17:215-219). May the painting of Venice at the beginning of this article be a modest tribute to this eminent cardiologist and accomplished painter and musician who loved Venice so much, witness his marvelous book of watercolors: Peter Harris. *The Bricks of Venice,* Bath, UK: The Old School Press; 2005.

To conclude, I would like to express my deep thanks to Professors Wolfgang and Jutta Schaper, my colleagues, and my family, for their friendship and support.
Remodeling: What Has Changed Over the Past 10 Years?
Summaries of Ten Seminal Papers

Pierpaolo Pellicori, MD, FESC
Department of Cardiology - Castle Hill Hospital - Hull York Medical School at University of Hull
Kingston upon Hull - HU16 5JQ - UK (e-mail: pierpaolo.pellicori@hey.nhs.uk)

1. Left ventricular remodeling after myocardial infarction: a corollary to infarct expansion
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Selection of seminal papers by Pierpaolo Pellicori, MD, FESC
Department of Cardiology, Castle Hill Hospital, Hull York Medical School at University of Hull, Kingston upon Hull, UK

Highlights of the years by Sherri Smith, PhD
Publications office
Previously, researchers have focused on the changes to the left ventricular structure after a myocardial infarction, and subsequently, the concept of “infarct expansion” was introduced. Infarct expansion is an event occurring within the initial hours and days post-myocardial infarction that progresses over weeks. These events are associated with poor exercise tolerance, more congestive heart failure symptoms, and increased mortality. Despite the amount of research conducted, few data were available regarding the noninfarcted segments during the recovery period. Therefore, McKay et al studied the fate of infarcted and noninfarcted segments of the left ventricle during the early recovery period after a transmural myocardial infarction.

A total of 30 patients (28 male; mean age, 55 years; range, 33 to 69) with their first ST-segment elevation myocardial infarction, who had been successfully treated with intracoronary or intravenous thrombolysis, were studied. A total of 15 patients had left anterior descending artery occlusion or subocclusion and 15 had right coronary artery occlusion, 15 had coronary artery disease restricted to one coronary artery in the infarction area and the other 15 had additional stenoses. Cardiac catheterization was performed at admission and 2 weeks later. All patients had patency of the culprit coronary artery with residual high-grade stenosis at the subsequent angiogram.

Compared with baseline, at the 2-week follow-up, there was a significant decrease in heart rate (P<0.03), left ventricular end-diastolic pressure (P<0.01), and pulmonary capillary wedge pressure (P<0.01). There were no changes in angiographic left ventricular ejection fraction or cardiac index; however, both left ventricular end-diastolic and end-systolic volumes increased, which were related to the extent of the initial myocardial infarction.

In those patients who presented a significant increase in the left ventricular end-diastolic volume, there was an increase in endocardial perimeter length in infarcted and noninfarcted segments (mean increase, 13% and 19%, respectively).

The following hypothesis recapitulates, in a simple and effective way, the results of this paper. Myocardial infarction leads to an increase in end-diastolic and end-systolic left ventricular volumes, with a subsequent increase in wall stress. Increased wall stress affects both the noninfarcted segment, causing hypertrophy and decreased contractility, and the infarcted segment, resulting in infarct expansion. These changes ultimately lead to late heart failure.

1986

Lady Gaga, American singer-songwriter and record producer, is born; the world’s largest butterfly farm opens on the Malaysian island of Penang; and the Diamond Jubilee of Shōwa, the 124th Emperor of Japan, is celebrated in Tokyo.
Risk of congestive heart failure and death is substantially augmented in patients with reduced left ventricular function and ventricular enlargement post-myocardial infarction. Treatment for acute myocardial infarction has significantly improved, leading to a reduction in the risk for left ventricular dysfunction, and an improved morbidity and mortality. Despite these advances, it is important to remember that there is heterogeneity in the patient population post-myocardial infarction and identifying those factors that positively influence the outcomes for a wider range of patients is necessary.

The HEART trial (Healing and Early Afterload Reduction Therapy) was a randomized, double-blind study of the hemodynamic effects of early vs delayed administration of three regimens of ramipril in 352 patients after myocardial infarction.

In this substudy, Solomon et al evaluated the extent and predictors of recovery of left ventricular function, only in the patients enrolled in HEART who underwent reperfusion (88%, 65% had thrombolysis alone, 13% had primary angioplasty alone, and 8% had both).

Patients underwent echocardiography within 24 hours post–myocardial infarction (before randomization to one of three different doses of ramipril) and again at 14 and 90 days after the acute event. Serial echocardiography was available for 249 patients at 1, 14, and 90 days post–myocardial infarction. A total of 12 patients died during follow-up. At 90 days post–myocardial infarction, 22% of patients, who had an abnormal ejection fraction on day 1, demonstrated a full recovery of left ventricular ejection fraction (LVEF >55%), 36% demonstrated a partial recovery, and 16% had a decreased ejection fraction of more than 5%. The majority of functional recovery occurred within 14 days post–myocardial infarction. Overall, left ventricular dilatation was inversely correlated with the improvement in ejection fraction over 90 days (r = -0.27, P<0.001). Of the measurements obtained at day 1 post–myocardial infarction, peak creatine kinase levels were the strongest independent predictor of functional left ventricular recovery. One major result from this study was that early measurements of LV function by echocardiography (∼24 hours post–myocardial infarction) are not the best predictors of future ventricular function; however, measurements taken after discharge or during an initial follow-up visit may more accurately predict long-term risks.

Recovery of ventricular function after myocardial infarction in the reperfusion era: the healing and early afterload reducing therapy study
Myocardial viability as a determinant of the ejection fraction response to carvedilol in patients with heart failure (CHRISTMAS trial): randomised controlled trial


Lancet. 2003;362:14-21

Morbidity and mortality associated with heart failure can be effectively reduced by treating patients with β-blockers. While the exact mechanism of action of β-blockers is not completely understood or fully elucidated, long-term use has been associated with a decrease in left ventricular volume and an increase in left ventricular ejection fraction (LVEF). This response occurs consistently in patients with dilated cardiomyopathy, but to a lower extent in patients with heart failure due to ischemic heart disease, which may indicate that there are variations in the substrate underlying left ventricular dysfunction. Therefore, Cleland et al assessed whether improvement in LVEF was associated with the volume of hibernating myocardium (ie, viable myocardium with contractile function).

In the CHRISTMAS trial (Carvedilol Hibernating Reversible Ischaemia Trial: Marker of Success), a multicenter, randomized, double-blind, placebo-controlled trial, the β-blocker carvedilol was compared with placebo in patients with chronic ischemic heart failure. The authors tested whether improvement in LVEF was related to the volume of hibernating myocardium. The primary end point was change in LVEF, which was measured by radionuclide ventriculography, in patients with hibernating myocardium (hibernators) vs nonhibernators. Hibernators were defined as having more than two hypokinetic segments with high uptake of technetium sestamibi (>60%) or one high-uptake segment with two anatomically adjacent segments whose uptake was 51% to 60%. All other patients were considered non- hibernators.

Of the 387 patients who were randomized, 82 dropped out of the study and the remaining 305 patients were analyzed. The mean LVEF was 30%±11, with an LVEF >50% in 4% of the patients. During follow-up, LVEF increased in patients randomized to carvedilol, but remained unchanged in the placebo group. Overall, the placebo-subtracted increase in LVEF with carvedilol was 3.2%, it was 3.6% (P=0.0002) in hibernators and 2.9% (P=0.011) in nonhibernators. Patients with more myocardium affected by hibernation alone or hibernation and ischemia had a greater increase in LVEF after taking carvedilol (P=0.0002 and P=0.009, respectively).

In a prespecified multivariable analysis, which included age, sex, presence of angina, treatment allocation, baseline LVEF, and hibernation status of the myocardium, only carvedilol use and a low LVEF independently predicted an increase in LVEF.
Important predictors of cardiovascular morbidity, which includes heart failure, are increased left ventricular mass and left ventricular hypertrophy. The CHS study (Cardiovascular Health Study), a large multicenter longitudinal study, investigated whether left ventricular mass is a risk factor for a subsequent decline in LVEF in individuals with preserved LVEF.

The CHS study included individuals older than 65 years who had echocardiograms performed at baseline and at a 5-year follow-up. Of the 5021 participants in the baseline cohort, 3042 had a normal baseline LVEF and an assessment of left ventricular mass by either echocardiography or electrocardiography.

Compared with patients with smaller left ventricular mass, those with greater left ventricular mass were older and more often men, with a higher prevalence of diabetes, hypertension, and coronary artery disease. They also had larger left ventricular and left atrial diameters.

At the subsequent 5-year follow-up echocardiography, 265 individuals (9%) developed a reduced LVEF. Around 14% of patients in the highest quartile of left ventricular mass had a reduced LVEF (vs <5% in the lowest two quartiles, \( P<0.001 \)). A reduced LVEF occurred more frequently in patients with greater left ventricular mass with or without an incident acute coronary event during follow-up.

Baseline echocardiographic and electrocardiographic assessment of left ventricular mass was independently associated with reduced LVEF at the 5-year follow-up in elderly individuals with a normal LVEF. Further studies are needed to determine the pathophysiological mechanisms resulting in the association between an increased left ventricular mass and development of a reduced LVEF, even in subjects without a prior myocardial infarction.

A 428 million-year-old fossil of Pneumodesmus newmani is identified as the world’s oldest known creature to have lived on land; Francis Crick, American Nobel laureate in Physiology for discovering the double helix structure of DNA, dies at age 88; and a decomposing sperm whale spontaneously explodes in Tainan city, Taiwan.
The prognosis of heart failure patients remains poor despite the advances in treatment regimens. Heart failure patients have regions of delayed myocardial activation and contraction, which leads to cardiac dyssynchrony. Several previous trials have demonstrated a decrease in symptoms and an improvement in exercise capacity, quality of life, and ventricular function when using cardiac resynchronization therapy. The CARE-HF trial (CARDiac RESynchronization-Heart Failure) was a multicenter, international, randomized trial that evaluated the effect on morbidity and mortality of standard medical therapy vs the combination of standard therapy plus cardiac resynchronization therapy in patients with left ventricular systolic dysfunction, cardiac dyssynchrony, and symptomatic heart failure.

A total of 813 patients with advanced heart failure (New York Heart Association [NYHA] class III or IV, severe left ventricular systolic dysfunction [left ventricular ejection fraction <35%], and cardiac dyssynchrony [QRS interval >120 msec]) were randomized to standard pharmacological treatment alone or the combination of standard therapy plus cardiac resynchronization therapy, and followed-up for a mean of 29 months (range, 18 to 45 months). The primary end point was a composite of all-cause death or an unplanned hospitalization for a major cardiovascular event.

Cardiac resynchronization therapy reduced the risk of the composite end point of all-cause death or unplanned hospitalization for a major cardiovascular event compared with standard therapy alone (39% vs 55%; hazard ratio, 0.63; 95% CI, 0.51-0.77, P<0.001). Patients receiving cardiac resynchronization therapy also had less severe symptoms (P<0.001) and a better quality of life at 90 days (P<0.001). Additionally, at the 3- and 18-month follow-up visits, cardiac resynchronization therapy led to an increase in the left ventricular ejection fraction, a decrease in the left ventricular end-systolic volume index (P<0.001 for both), and a decrease in the area of mitral regurgitation (P=0.003). The CARE-HF study showed that, in addition to standard therapy, cardiac resynchronization is an effective therapy for patients with left ventricular systolic dysfunction and cardiac dyssynchrony.
One of the most important risk factors for cardiovascular disease is age, however, there is an incomplete understanding of the mechanisms involved in the predisposition to cardiovascular morbidity and mortality. While left ventricular hypertrophy is well known to be associated with age, it is still unknown to what extent this remodeling is associated with age-specific changes in left ventricular mass, volume, chamber performance, and intrinsic myocardial function. In order to analyze the age-associated changes in left ventricular structure and function, Cheng et al used cardiac MRI to determine whether these changes predict cardiovascular outcomes.

A total of 6814 individuals (aged between 45 and 84 years, representing four ethnic groups [non-Hispanic white, black, Hispanic, and Chinese], who had no clinical history of cardiovascular disease (ie, coronary artery disease, peripheral arterial disease, cerebrovascular disease, or heart failure)) were enrolled in the MESA study (Multi-Ethnic Study of Atherosclerosis). Of these, 5004 participants had a cardiac MRI, and for the analysis, they were divided into eight age groups.

With increasing age, left ventricular end-diastolic volumes (LVEDV) decreased in men and women, but left ventricular ejection fraction (LVEF) modestly increased, which was accompanied by a decrease in stroke volume and systolic strain and a worsening diastolic function. An incremental decline in left ventricular mass across age groups (~0.3 g per year, \(P<0.0001\)), with an increase in the mass-to-volume ratio (+5 mg/mL per year, \(P<0.0001\)) was also observed in both sexes. Over a median follow-up of 4 years, there were 180 cardiovascular events (45 myocardial infarctions, 71 episodes of angina, 48 cases of heart failure, 39 strokes, and 13 deaths due to coronary artery disease) in 4968 participants (36 lost to follow-up). Increased left ventricular mass-to-volume ratio was associated with a higher risk of adverse outcomes (hazard ratio, 1.23; 95% CI, 1.09-1.39; \(P=0.001\)).

In this large cohort of well-characterized individuals with no known previous cardiovascular disease, age was associated with a peculiar phenotype of left ventricular remodeling (increasing left ventricular mass-to-volume ratio), with impaired left ventricular strain and diastolic function despite having a preserved LVEF, which confers a greater risk of adverse cardiovascular outcomes.

The first animal from an extinct species to be recreated by cloning, a Pyrenean ibex, is born alive, but dies 7 minutes later due to physical defects in its lungs; the American astronomer John Allen Eddy dies at age 78; and Patriarch Kirill of Moscow is enthroned as the Patriarch of the Russian Orthodox Church.
Prevalence and significance of alterations in cardiac structure and function in patients with heart failure and a preserved ejection fraction


Circulation. 2011;124:2491-501

Pathophysiological changes in cardiac structure and function, ie, progressive left ventricular dilation, eccentric remodeling, and systolic dysfunction, have been identified in patients with heart failure with a reduced ejection fraction (HFREF). However, the pathophysiological mechanism responsible for the development of heart failure with preserved ejection fraction (HFPEF) has only been partially defined. Currently, it is still challenging to diagnose patients with HFPEF. However, the diagnostic criteria should involve inclusion criteria that reflect the changes in cardiac structure and function. Delineating the relationship between structural remodeling, functional changes, and clinical outcomes may add prognostic value to the diagnosis.

Zile et al conducted a large echocardiographic substudy of the I-PRESERVE trial (Irbesartan in heart failure with PRESERVED systolic function) to examine whether echocardiographic changes in cardiac structure and function in patients with HFPEF were associated with morbidity and mortality.

A total of 4128 patients with HFPEF were enrolled in I-PRESERVE. Briefly, the inclusion criteria comprised: (i) age ≥60 years, (ii) left ventricular ejection fraction (LVEF) ≥45%, and (iii) recent hospitalization for heart failure. From these patients, 745 were also enrolled in this substudy, whereby a complete echocardiographic assessment was taken before randomization. To be eligible for the echocardiography substudy, patients had to be in sinus rhythm at baseline.

More than 95% of patients studied had a normal left ventricular size and volume. A total of 7% of patients had an LVEF <50%; however, longitudinal systolic function was abnormal in 14% of cases. Left ventricular hypertrophy or concentric remodeling was present in 59% of patients and the majority of patients had only mild left atrial enlargement (51% compared with the 15% who had a moderate or severe dilatation). Only 4% of patients had severe diastolic dysfunction at Doppler echocardiography, which was normal in 31% of the cases.

Independent predictors of adverse outcome (primary end point, death, or protocol-specific cardiovascular hospitalization) were increasing left ventricular mass and hypertrophy and an enlarged left atrial area, but not the E/E’ ratio (the relation of peak early diastolic filling velocity to mitral lateral and septal annular tissue velocity during early filling).

This study resulted in two main findings: (i) patients with HFPEF, who were in sinus rhythm, had a high prevalence of structural remodeling, and (ii) the structural remodeling changes were independently associated with an increased morbidity and mortality risk, which was significantly increased even after including known risk factors (ie, N-terminal fragment of the prohormone brain natriuretic peptide) in the multivariable analysis.
Heart failure is a common and ever increasing problem that is still associated with a poor prognosis despite advances in treatment regimens, especially for patients with left ventricular systolic dysfunction—otherwise known as reduced left ventricular ejection fraction (LVEF). Many patients with primary left-sided heart failure consequently develop secondary right ventricular dysfunction. Clinical diagnosis of heart failure is complicated, as it requires evidence of cardiac dysfunction in the presence of symptoms; however, the cardiology community needs a broader view of what constitutes cardiac dysfunction. One hallmark of heart failure is congestion, possibly making distension of the great veins the best marker. The inferior vena cava (IVC) distends as the right atrial pressure increases; therefore, it may serve as an index of heart failure severity, independently of LVEF. As such, the IVC may reflect the level of right atrial pressure and the status of a (dys)functional right ventricle.

In this echocardiographic study, 568 patients with symptoms and signs of heart failure, along with objective evidence of cardiac dysfunction (either LVEF <45% or the combination of a dilated left atrium ≥4 cm and elevated N-terminal fragment of the prohormone brain natriuretic peptide [NT-proBNP] ≥400 pg/mL), were enrolled with a median follow-up of approximately 1.5 years.

Despite having a similar LVEF among tertiles of IVC diameter, patients in the highest tertile (larger IVC) were older, with a lower body mass index, and they were more likely to have atrial fibrillation and have received treatment with diuretics. They had worse symptoms, more signs of congestion, and higher NT-proBNP plasma levels. At echocardiography, left atrium diameters and volumes were larger, and right ventricular dysfunction was more severe, with higher pulmonary artery systolic pressure. Increasing age, log NT-proBNP, left atrium volume, and pulmonary artery pressure were independent predictors of increasing IVC diameter.

IVC diameter remained the strongest predictor of adverse prognosis in the univariable analysis and had a similar power to predict prognosis at 1 year when compared with NT-proBNP. Patients in the highest tertile of IVC diameter (median, 24 mm; interquartile range [IQR], 23-27 mm) had a 7-fold greater risk of being hospitalized for heart failure or dying from a cardiovascular cause than patients in the lower IVC tertile (median IVC, 16 mm; IQR, 15 to 16 mm).

The results of this study suggest that ultrasound assessment of the IVC identifies outpatients with heart failure who have a higher risk of an adverse outcomes.
Severe mitral regurgitation is associated with left atrial remodeling and enlargement, which is accompanied by mechanical stress, cellular hypertrophy, and interstitial fibrosis, and eventually, left atrial failure. In this study, Cameli et al evaluated the correlation between left atrial longitudinal function (measured by the peak atrial longitudinal strain at speckle tracking [PALS]) and the histopathological changes of the left atrial walls found at biopsy in patients with severe mitral regurgitation undergoing surgical repair.

A total of 46 patients (mean age, 69; 47% women) with severe mitral regurgitation due to mitral valve prolapse, who were undergoing corrective mitral surgery, were enrolled in the study. Samples of the left atrial free wall were obtained during cardiac surgery in all patients.

A strong negative correlation was found between global PALS and both the histological degree of left atrial myocardial fibrosis ($r=-0.82; P<0.0001$) and the left atrial endocardial thickness ($r=-0.66; P=0.0001$). No relationships were found between the extent of left atrial fibrosis and left ventricular ejection fraction ($r=-0.07; P=NS$) or the $E/E'$ ratio (relation of peak early diastolic filling velocity to mitral lateral and septal annular tissue velocity during early filling; $r=0.14; P=NS$) at echocardiography. Global PALS, left atrial indexed volume, left atrial ejection fraction, and left atrial area were shown to be independently associated with left atrial fibrosis according to a stepwise multivariate analysis (overall $R^2=0.70; P<0.0001$). Global PALS accounted for more than 66% of the total variability explained by the model, indicating that it had the best diagnostic accuracy to detect left atrial fibrosis (area under the curve, 0.89).

This study provided a new understanding of the structural remodeling events that occur in patients with mitral valve disease, as well as demonstrating that global PALS is more sensitive than traditional echocardiographic markers of left atrial size and function for detecting left atrial fibrosis. However, additional trials are necessary to improve the study of left atrial function with speckle tracking.
Diagnosing heart failure requires combining clinical features (e.g., breathlessness) and objective evidence of abnormal cardiac function (e.g., increases in plasma concentrations of natriuretic peptides). Typically, the diagnosis of heart failure is simpler in patients with a reduced left ventricular ejection fraction (LVEF), however, not all patients fall into this category as some have a normal ejection fraction and possibly other abnormalities, including a dilated left atrium. A dilated left atrium indicates a greater risk of adverse cardiovascular outcomes for patients with heart failure, irrespective of their LVEF. Assessment of the left atrium is often accomplished using transthoracic echocardiography, but it may lack accuracy; therefore, other imaging techniques, such as cardiac magnetic resonance imaging (cardiac MRI) or computer tomography, may be used.

In this cardiac MRI study, Pellicori et al evaluated the left atrial volume and function (emptying function; LAEF) in 664 individuals in sinus rhythm who had symptoms or signs of heart failure and objective evidence of cardiac dysfunction (either an LVEF <50% on cardiac MRI or increased plasma concentrations of the N-terminal fragment of the prohormone brain natriuretic peptide [NTproBNP] >400 pg/mL [or >125 pg/mL, if patients were taking loop diuretics]). The primary outcome was a composite of hospitalization for heart failure and all-cause mortality. Compared with patients with a better LAEF (56%, interquartile range [IQR], 53% to 61%), patients with a lower LAEF (23%, IQR, 17% to 28%) also had worse kidney functions, lower body mass index, higher plasma concentrations of NTproBNP, and were taking more loop diuretics. They also had a lower left and right ventricular ejection fraction and a greater left and right ventricular mass. Decreasing LVEF and increasing NTproBNP were independent predictors of decreasing LAEF. During a median follow-up of more than 2 years, 394 patients (59%) with heart failure died or they were admitted for heart failure, and 101 patients (15%) developed atrial fibrillation. LAEF, but neither LVEF nor left atrial volumes, was an independent predictor of adverse outcomes.

The results of this study suggest that, in patients with heart failure, a lower LAEF is associated with higher plasma concentrations of natriuretic peptides and an adverse prognosis.

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Left atrial function measured by cardiac magnetic resonance imaging in patients with heart failure: clinical associations and prognostic value


Eur Heart J. 2015;36:733-742

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## Remodeling: What Has Changed Over the Past 10 Years?

### Bibliography of One Hundred Key Papers

selected by **John G. F. Cleland, MD, PhD, FRCP, FESC, FACC**

*Royal Brompton & Harefield Hospitals - Imperial College - London - UK*  
(e-mail: j.cleland@imperial.ac.uk)

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Prevalence and significance of alterations in cardiac structure and function in patients with heart failure and a preserved ejection fraction.  
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