FEATURED TRANSLATIONAL AND INTERVENTIONAL STRATEGIES IN THE MULTIDISCIPLINARY MANAGEMENT OF HEART FAILURE

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To Sonia, Radko and Christine,
To my parents,
To my family,
To my colleagues and friends:
Thanks to your sacrifices and unconditional support,
I have been able to expand my professional horizons,
To give my best to innovation and new knowledge
And better serve to my patients.
I humbly thank you all.
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1. **INTRODUCTION AND CONCEPTS**

The World Health Organization recognizes the emergence of non-communicable diseases, in particular heart failure, as the leading cause of morbidity and mortality. The American Heart Association in the most recent Heart Disease and Stroke Report underscores that cardiovascular conditions account for 1 of every 2.9 deaths in the United States. More than 2,200 Americans die of cardiovascular disease each day, an average of 1 death every 39 seconds. Indeed, heart failure is one of the most prominent challenges to public health. Modern management of acute myocardial infarction with rapid revascularization has reduced early mortality but has precipitated the incidence of chronic heart failure among survivors, an epidemic that is anticipated to expand worldwide accelerated by the pandemic trends of ischemic heart disease and the aging of the global population.

Recurrent hospitalizations and premature death, prevalent in this ever growing patient population, have imposed a major unmet need associated with the inability of current, largely palliative therapies to address massive tissue destruction post-infarction. The myocyte-deficit in infarction-induced heart failure is in the order of 1 billion cells with a 25% loss of the left ventricular mass. A hallmark of this malignant pathology is the progressive maladaptive remodeling of the infarcted myocardium that perpetuates systolic and diastolic dysfunction, and ultimately leads to the overt syndrome of congestive organ failure. The rise in mechanical load activates a cascade of deleterious neuro-humoral signaling pathways and multiple cellular and molecular abnormalities such as alterations in extracellular matrix and vascular elements occur with left ventricular remodeling as a final result. The term left ventricular remodeling reflects changes in ventricular mass, its composition, volume overall geometry and shape. During the process of remodeling, the left ventricle becomes less elliptical and ventricular sphericity increases. These changes in shape, contribute to the reduction in radial, circumferential and longitudinal strains. Also the torsion mechanics is being altered, apical segments do not retain maximal curvature and the apex is no longer an optimum fulcrum for ventricular contraction.

Multimodal treatments have been introduced to alleviate the symptoms or reverse the progression of heart failure. Given the causal relationship between remodeling and
reduced pump function, therapies that decrease the elevated stress are of utmost important in the management/treatment of heart failure. In this regard, term “reverse remodeling” has been adopted to reflect beneficial effects of those therapeutic intervention that induce a leftward shift in the ventricular pressure-volume relationship in parallel with ventricular size reduction. This remodeling process has also been linked to favorable changes in the molecular and cellular signature and is distinct from cardiac recovery, which is defined as the best achievable clinical outcome of a patient with heart failure, namely being free from future heart failure events. Though not all therapies inducing reverse remodeling alter long-term prognosis, every therapy associated with a positive long-term outcome and cardiac recovery has been paralleled by reduction in ventricular volumes.

Here, we wish to feature several concepts of modern approaches in the multidisciplinary management of heart failure. We wish to provide critical and yet forward looking evaluation of the emerging translational concepts and device-based strategies as they could be beneficial for graduate and postgraduate clinicians and researches with interest in heart failure. Their awareness can guide the holistic and yet personalized, precision aimed bedside care in the real world clinical practice.

The scriptum will initially feature the pragmatic rules in the clinical approach to a patient presenting with heart failure. Ensuing chapters will highlight the potential of biomarkers in diagnosing heart failure and its progression. Heart failure with preserved ejection fraction with its increasing prevalence is dominating in the spectrum of cardiac disease. However, its detection and accurate diagnosis remains challenging. We provide here a case-based practical approach to its evaluation using the clinical Doppler echocardiography. Dyssynchronous heart failure represents a distinct phenotype in heart failure with reduced ejection fraction. Cardiac resynchronization therapy has gained the class I evidence and is the only causative therapy to address this entity potentially leading to the survival benefit and functional improvement. We detail the phenotypic, cellular and molecular features of the dyssynchronous heart failure in comparison to overt heart failure. Likewise, functional mitral regurgitation has been recognized as one of the key determinants of morbidity and mortality in chronic heart failure. Yet, the management and decision to intervene remains challenging. Accordingly, a dedicated chapter provides the readers with the practical guidance in various situations of real world practice. Despite undisputable advances in current existing standard of care in heart failure resulting in
improved survival rates and reduced morbidity, a gap persists in the therapeutic options in patients with advanced heart failure. The clinical need to fill this gap stimulates the search for novel therapies thanks to refined understanding of the molecular pathophysiology of heart failure in tandem with technological advances in the device development. In addition to cardiac resynchronization, novel device-based interventions are emerging to tackle elements of the heart failure progression ranging from ventricular reshaping to neurohumoral modulation. Likewise, rapid progress of fundamental cell biology and regenerative medicine holds the promise for advancing the existing armamentarium of therapeutic interventions in heart failure. The rationale and potential of the new field of device-based interventions as well as regenerative cardiovascular medicine in the multidisciplinary is critically featured in the remaining chapters.

The awareness should help to facilitate the adoption of the personalized precision medicine and yet recognizing the need for the holistic approach in the management of heart failure.
2. “COMMANDMENTS” OF THE BEDSIDE CARE IN THE REAL WORLD OF HEART FAILURE MANAGEMENT

Despite the existing evidence and professional guidelines, the diagnostic and therapeutic management of heart failure remains challenging. This paradoxical position relates to increased prevalence of heart failure due to aging with co-morbidities, multifaceted clinical presentations and developing standard of care population. The broadening scope of problem is paradoxically faced by trends in the professional training with increasing super-specialization with physician suboptimally trained in the global, “holistic” approach to the patient’s problem. Growing number of professional guidelines, incritical confidence in their validity and their blind application creates a danger of the scotomic clinical evaluation threatening paradoxically the well being of the patient. Likewise, increased availability of advance technologies requires their critical positioning within the clinical care. Accordingly, this chapter will provide with few practical tips on approaching the patient with heart failure.

Facing a patient with heart failure symptoms one should ask following basic questions

1. Has the patient underlying heart failure?
2. What is the underlying mechanism?
3. Is heart failure the main problem of the patient?
4. How to get out of it and secure the patient’s benefit?

The decision making starts with the careful review of the patient’s complete medical history with attention for obtaining original images and assessment and not only relying on the written reports. Such critical review is important for evaluation of noninvasive imaging or catheterization data. Combine use of the medical history, clinical evaluation, use of appropriate imaging and laboratory analyses can be the diagnosis of heart failure fairly certain

At this early stage, poised clinical approach should not get distracted by the “organ” specific focus. Instead, clinical evaluation should retain holistic view and determine whether the “cardiac pathology is the main problem”. Question such as whether the cardiac pathology is primarily responsible for the clinical situation, it is the primary problem or only
a bystander, is it accounted for the worsened quality of life should be upfront asked. Such holistic approach underscores the imperative of the multidisciplinary assessment of patient with heart failure.

After clarifying above mentioned questions, the steps should be taken to search for the “way out of the problem” and search for the precipitating and correctable factors in parallel with the optimization of the therapeutic management. In this regard, societal guidelines are helpful, however, they should not be “blindly” followed and overemphasized when facing the individual patient who often does not represent the patient population used to built the evidence within the guidelines recommendations.

Precipitating factors. The first step is to understand the mechanism of heart is to identify factors that might have triggered the heart failure symptoms. The careful recent history is often revealing in this regard. Likewise, the understanding the precipitating factors is important in the forward looking preventive measures after re-compensation. Table summarizes the most frequent precipitating factors leading to heart failure symptoms.

Correctable causes of heart failure. The analysis of the precipitating factors is also critical for identification of the correctable causes of heart failure. These factors are extensively discussed in the traditional textbooks. Here, we wish you list those sometimes overlooked:

I. Atrial fibrillation or atrial flutter. When facing the patient with heart failure and atrial fibrillation or flutter it is often impossible to distinct whether the arrhythmia, especially in case of increased ventricular rates, is the consequence or cause of the current heart failure symptoms. In general, the contribution of “tachycardiomyopathy” to reduced left ventricular function is unpredictable though it is often associated with absence of major left ventricular dilation. Pragmatically, if atrial arrhythmia has not been known in the last year prior to onset of symptoms, every attempt should be made to restore sinus rhythm after reasonable recompensation. Class I and III antiarrhythmics with exception of amiodarone are to be avoided. In younger patient, betablockers are preferred given the amiodarone toxicity. In case of elderly patients with heart failure and normal ejection fraction, atrial fibrillation can be attempted to reconverted without antiarrhythmics after achieving euvoletic conditions.

II. Conduction abnormalities. The presence of left bundle branch block with prolonged QRS interval in case of heart failure gained the class I recommendation
for cardiac resynchronization therapy in patients with severely reduced left ventricular function. Particular attention should be paid to patient with heart failure and permanent right ventricular pacing. The particular attention should be paid to those who were having normal cardiac function prior to pacemaker implantation. In these cases, attempts should be taken to restore the native conduction either by pacemaker reprogramming or changes in the medical regimen aimed to reduced the effects of bradycardia inducing agents such as digitalis or even betablocker. If not leading to the improvement, consideration of biventricular pacing is indicated. In addition, various program-related issues such as pacemaker movement tachycardia, mode switch failure due to inappropriate sensing of atrial fibrillation, short or adaptive AV delays, rate responsive programming lead also to excessive right ventricular pacing and should be corrected.

III. **Aortic valve stenosis.** This valvular heart disease can be initially overlooked at routine clinical exam especially in elderly when systolic murmur is weak. Likewise, it may be underestimated due to low-flow, low gradient situation. This condition may be challenging to manage and pharmacological stress test is mandatory to unmask the significance of the valvular stenosis. One should bear in mind that low ejection fraction is not synonymous to low flow over the aortic valve and that that transvalvular aortic gradient correlated with stroke volume and not ejection fraction. In other words, to exclude significant aortic stenosis, one should perform not only the stress echocardiography to evaluate the rise in the transvalvular gradient. The stress echo doppler study should be complemented with right heart catheterization and assessment of the venous saturation. If the mixed venous saturations remains normal or high, significant aortic stenosis is less likely and surgery may not yield expected improvement.

IV. **Constrictive pericarditis.** Constrictive pericarditis is often unrecognized in patients with predominant signs of right heart failure. It represents an extreme model of diasotolic heart failure. It should be Constrictive pericarditis may still be a difficult diagnosis. It is an extreme model of heart failure with impaired diastolic function and beta-blocking agents are relatively contra indicated and ill
supported. It should be considered in case of chronic heart failure with absence of severe pulmonary hypertension.

The medical and interventional management has been expanded in the last 30-40 years with solid evidence for benefits of traditional medical therapy or interventions such as revascularization. Yet, clinicians often face situation where the guidelines recommendations are unclear or not fully applicable in the real world patient population. Following section will highlight several practical consideration in the medical and interventional management:

I. **ACE inhibition (I) and Angiotensin receptor blockers (ARB).** International guidelines emphasize the need to achieve the “target” dose of ACEI or ARB as tested in the clinical trials demonstrating beneficial survival effect. However, evidence supporting this statement is not strong. In fact, only ATLAS trial compared the low and high dose on the survival in patients with low left ventricular ejection fraction. The study demonstrated no mortality benefit in high dose lisinopril group. In real world clinical practice, it remains challenging to titrate the dose of ACEI or ARB to maximal dose in heart failure patients on concomitant betablocker therapy due to hypotension. In our practice, we start the low dose of ACEI or ARB but we prefer to preferentially titrate the betablockers due to their stronger beneficial effects on mortality and remodeling.

II. **Betablockers.** Given the survival benefits, betablockers are the main pillar of the heart failure treatment. They should be always attempted after achieving reasonable clinical re-compensation. Consequently, one should avoid to stop them abruptly. It is very seldom that betablockers would not be possible to start or increase the dose in the chronic heart failure. The failure to start the betablocker indicate most likely on inadequate assessment of the clinical problem or inappropriate timing if patient is still volume overloaded or having low blood pressure to inadequately high dose of ACEI/ARB. On the other hand, in rare situation, betablockers needs to be critically evaluated and better avoided such as patient with critical aortic stenosis and heart failure or severe end-stage heart failure with low cardiac output. Here, individual case per case evaluation is required.
III. **Aldosterone blockers.** While their benefits in heart failure with preserved ejection fraction are debated, aldosterone antagonists belong to additional pillar of the heart failure treatment in patients with low ejection fraction. They are often omitted or withdrawn due to their side effects such as gynecomastia, renal worsening or hyperkalemia. Careful titration with regard to the patient condition his renal function should be utilized in their implementation within the heart failure medical regimen. Hyperkaliemia as such should not be the reason for discontinuation. In contrary its detection should be critically evaluated from the point of potential hemolysis of blood samples. If detected and in the presence of preserved or reasonable control of the renal function anion exchanger are to be added to balance the kaliemia. In our practice, we keep the aldosterone blockers also after patient returns to low NYHA class, a practice supported also by the EMPHASIS trial.

IV. **Myocardial revascularization.** Assessment of the coronary anatomy and presence of ischemia is one of the key diagnostic steps in the heart failure management. The management is challenging mainly in heart failure patient presenting without the anginal symptoms. The benefits of revascularization in such patients are questioned based on the results of the STITCH trial. The critical evaluation of this trial is beyond the scope of this work. Nevertheless, several caveats are to be kept in mind before generalizing the results of this trial to the real world practice. The trial suffered from several methodological shortcomings, its design and inclusion criteria were changed during the course of the trial. Leaving the issue of the left ventricular reshaping apart, the decision to revascularize needs to be tailored to the individual patient, considering his co-morbidities and taking into account a holistic approach (Figure 2.1) were multiple factors are weighed in for the ultimate decision making to revascularize.
V. **Functional mitral regurgitation.** Functional mitral regurgitation contributes to increased morbidity and mortality in chronic heart failure. The clinical dilemma is given by this evidence and yet lack of conclusive data demonstrating the benefits of mitral valve intervention in the setting of heart failure on survival. The tailored management is specifically discussed in the separate chapter.

VI. **Restoration of sinus rhythm.** Substantial proportion of heart failure patient with reduced left ventricular function presents with atrial fibrillation or flutter. As mentioned above, in case of recent onset, we systematically attempt for cardioversion after achieving euvoletic conditions and general optimization of the medical therapy. On the other hand, if sinus rhythm cannot be achieved or patient has been know with episodes of atrial fibrillation and not associated with heart failure symptoms, rate control strategy can be considered.
VII. **Medical overtreatment.** Multimodal pharmacology is frequent in heart failure patients. They are typical older, have several co-morbidities requiring various pharmacological management. The overall medical therapy has to be critically evaluated from the pharmacological perspective of potential drug interaction. The role of clinical pharmacologist is here often underestimated. In addition, medical regimen should be also continuously evaluated as the patient is being re-compensated or the favorable left ventricular remodeling has been achieved. This in particular case for re-evaluation of the dosing of loop diuretics.
3. **BIOMARKERS IN HEART FAILURE: BRAIN NATRIURETIC PEPTIDE AND BEYOND**

The diagnosis of heart failure is based on the clinical assessment with the important role of imaging to diagnose left ventricular dysfunction or overload. However, prognosis or response to treatment in individual patients with similar degree of left ventricular dysfunction individually often differs. The clinical need of refining the diagnosis, patient stratification as well as therapeutic monitoring has sparked continuous search for biomarkers as useful tools in the heart failure management. Such biomarkers should aid the clinicians by being rapidly available on repetitive basis. They can be schematically divided into four categories: biomarkers of myocardial stress or injury, biomarkers of neuro-humoral activation, biomarkers of cardiac remodeling and markers of co-morbidities (Table 3.1). Brain natriuretic peptide (BNP) is the most established biomarker routinely used in the clinical practice to diagnostic and stratify patients with heart failure. In addition to this biomarker, the current chapter provides also insights into other clinically available markers and their integration into the state-of-the-art heart failure management.

**Table 3.1** Biomarkers in heart failure reflecting various mechanisms involved in heart failure onset and progression

![Table 3.1 Biomarkers in heart failure reflecting various mechanisms involved in heart failure onset and progression](image)
**BNP processing and structure.** Human brain natriuretic peptide is an established biomarker in heart failure. It belongs to the category of cardiac-specific markers being released by heart in response to myocardial stress. The peptide is synthesized as a 134 aminoacid peptide that is subsequently processed to form a 108 aa peptide (proBNP). The proBNP is enzymatically cleaved by corin, a transmembrane serine protease produced in cardiomyocytes to form a 76-aa N-terminal NT peptide (Nt-proBNP) and a biologically active 32-aa C-terminal peptide (BNP). They are both released into the circulation. The biologically active BNP, the intact 108 amino acid proBNP and the remaining part of the prohormone NT-proBNP all circulate in the plasma and can be measured by commercially available immunoassays. They bear diagnostic and prognostic relevance, may track the therapeutic response and testing is recommended in the professional guidelines.

The physiologic effects of BNP are exerted by binding to the natriuretic peptide receptor type A. It contains a guanylate-cyclase domain leading to the production of cGMP and the activation of its downstream signaling cascade. Venous and arterial vasodilation, maintenance of appropriate intravascular volume by promoting natriuresis, opposing activation of the rennin-angiotensin-aldosterone system, reduced secretion of endothelin and attenuation of the central and peripheral sympathetic activity all have been attributed to BNP activation and are thought to be beneficial in heart failure.

However, in humans with overt heart failure and high BNP levels assessed using conventional assays, the expected cardiovascular and renal effects appear to be reduced despite elevated levels and overt HF patients display fluid and salt retention. The biological basis for the natriuretic peptide resistance is multifactorial: densensitization and downregulation of the natriuretic peptide receptor type A, upregulation of phosphodiesterase 5, leading to enhanced sGMP activation, and augmented neutral endopeptidase activity. Recently it was hypothesized hat abnormal proBNP processing may occur and that alternate less bioactive forms of BNP and Nt-proBNP circulate in patients with overt heart failure and account for this paradox. The abnormal processing appears to be related to increased levels exopeptidase dipeptidyl-peptidase (DPP) 4 in heart failure. This peptidase is present in numerous cell types including the vascular bed and cleave many bioactive peptides.

Although atrial and to a greater extent ventricular cardiomyocytes constitute the major source of BNP related peptides, recent data demonstrated that other cells such as
cardiac fibroblasts can also produce BNP. Additional neurohormones may stimulate cardiac BNP production in interplay between different cardiac cell types. The interaction between DPP-4 and BNP may have clinical relevance for both monitoring of BNP levels as well as in the biological action of BNP peptide. On one hand, commercially available assays appear to cross react with various molecular forms of BNP including the cleaved products. The Biosite and Shionogi assays detect the biologically active forms of BNP (BNP1-32 or 3-32) they do not measure Nt-BNP (1-76) or unprocessed BNP (1-108). On the contrary, the Roche Nt-proBNP assay measures Nt-proBNP (1-76), does not cross react with mature BNP1-32 or BNP 3-32 but does demonstrate significant cross-reactivity with unprocessed BNP 1-108. Note, neutral endopeptidases such as neprilysin also contribute to the degradation of BNP. It is of note that the novel drug LCZ696 inhibits the enzyme leading to an increase of BNP levels potentially clouding the use of BNP assays in the management of patients treated with this drug. The endopeptidase inhibition has not effect on the NT-proBNP levels. Finally, given the renal clearance, the circulating levels of BNP and NT-proBNP are influenced by the rates of glomerular filtration.

**BNP monitoring in heart failure management.** Circulating BNP levels can rapidly rise in response to increased myocardial stretch and intraventricular wall stress. The rapid elevation of BNP levels bears a high diagnostic accuracy in detecting the onset of acute heart failure. It is critical to point out that the elevated detection of elevated levels does not diagnose the heart failure per se. They should be used to support the clinical assessment being particularly helpful in unclear clinical situation. Depending the assay of choice, the cutoff values for BNP levels and NT-proBNP the detection of BNP levels above 100 pg/mL or age-stratified NT-proBNP levels were established to guide the clinical decision making (Table 3.2 and 3.3).

**Table 3.2** Single cut-off BNP and NT proBNP values to diagnose heart failure (HF)

<table>
<thead>
<tr>
<th></th>
<th>To exclude acute HF</th>
<th>To identify acute HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP</td>
<td>&lt; 30-50 pg/mL</td>
<td>&gt; 100 pg/mL</td>
</tr>
<tr>
<td>NT proBNP</td>
<td>&lt; 300 pg/mL</td>
<td>&gt; 900 pg/mL</td>
</tr>
</tbody>
</table>

Modified from Januzzi et al., Circulation 2012
### Table 3.3 Multiple cut-off BNP and NT proBNP values to diagnose heart failure (HF)

<table>
<thead>
<tr>
<th></th>
<th>Acute Dyspnea</th>
<th>Outpatient Setting</th>
</tr>
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<tbody>
<tr>
<td><strong>BNP</strong></td>
<td>&lt; 100 pg/mL to exclude</td>
<td>20 pg/mL (asymptomatic</td>
</tr>
<tr>
<td></td>
<td>100-400 pg/mL grey zone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 400 pg/mL to rule in</td>
<td></td>
</tr>
<tr>
<td><strong>NT-proBNP</strong></td>
<td>&lt; 450 pg/mL for &lt; 50 yrs old</td>
<td>&lt;125 pg/mL for &lt; 75 yrs old</td>
</tr>
<tr>
<td></td>
<td>&lt; 900 pg/mL for 50-75 yrs old</td>
<td>&lt; 450 pg/mL for ≥75 yrs old</td>
</tr>
<tr>
<td></td>
<td>&lt; 1800 pg/mL for &gt; 75 yrs old</td>
<td>or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 50 pg/mL for &lt; 50 yrs old</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 75 pg/mL for 50-75 yrs old</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 250 pg/mL for &gt; 75 yrs old</td>
</tr>
</tbody>
</table>

*Modified from Januzzi et al., Circulation 2012*

These cut-off values should be cautiously interpreted in several clinical situations. On one hand, the lower than expected levels are possible in patients presenting with heart failure with preserved ejection fraction as compared to patients with reduced ejection fraction. Obesity is also typically associated with lower than expected BNP or NT-proBNP levels. In such patients, the clinical judgment should drive the biomarker interpretation. On the other hand, higher BNP or NT-proBNP levels are also found in other cardiovascular diseases such as acute coronary syndromes, LV hypertrophy or hypertrophic cardiomyopathies or valvular heart disease. The levels can be elevated in response to cardiotoxic drugs, in patients with fast supraventricular arrhythmias or those presenting with pulmonary embolism or pulmonary hypertension. Caution should be taken with interpretation of elevated levels in patients with chronic renal insufficiency, stroke, advanced age (see age-adjusted cut off values in Table 3.3) or high output status. Likewise, as alluded therapy with neprilysin inhibitors leads to pharmacological increase of BNP values.
Both BNP and NT-proBNP levels bear a prognostic value in heart failure. The increased values either at admission or at discharge are associated with increased mortality. In addition, the dynamics of BNP values during the admission or serial changes throughout the treatment period provide even more accurate prognostic information for later mortality or repeat hospitalization (OPtimize HF trial and ValHeFT study). Given this evidence as well as reduction of BNP in response to the treatment set the basis for the biomarker-guided management in addition to the clinical assessment. Such approach could improve medical optimization and advance the dedicated outpatient heart failure management. The merit of the NT-proBNP guided care is now being studied in the randomized controlled trial (GUIDE-IT).

Other biomarkers in heart failure management. Despite broad adoption of natriuretic peptides as benchmark biomarker in heart failure, detailed understanding of molecular mechanisms in heart failure helped to accelerate other markers detecting or characterizing heart failure. As summarized in Table 3.1 they range from cardiac specific to noncardiac and reflect activation the complex interplay of myocardial stress/injury, neurohumoral activation, cardiac remodeling or involvement of co-morbidities such as renal failure.

Troponins, used to diagnose myocardial infarction, are often increased in heart failure as a marker of myocardial stress and injury. Their sustained elevation does not necessarily reflect myocardial necrosis, but it also point at ongoing apoptosis. The troponin assessment can be of value namely in diagnosing and follow-up of infiltrative disease such as amyloidosis.

Neurohumoral activation is one of the hallmarks of heart failure. Though catecholamine activation did not reach the clinical acceptance several novel markers reflecting prolonged neurohumoral activation such as adrenomedullin. Adrenomedullin is found in many tissues and organ systems where it functions as a circulating hormone as well as a local autocrine and paracrine effector. Its circulating levels were elevated in HF and related to reduced function or increased congestion. Adrenomedullin itself is unstable in vitro and a commercial assay measuring the mid-regional portion of the stable prohormone of ADM, MR-proADM, has been developed. Its elevated levels are emerging as a strong predictor of clinical outcomes even when added to BNP or NT-proBNP.

G protein coupled receptors are critically regulators of cardiac contractility which function is regulated by kinases (GRKs). These proteins are critical for contractile function by affecting
through receptor desensitization and down-regulation. GRK2 activity monitoring in various phenotypes of heart failure and development of a standardized assay may close the gap in biomarkers by analyzing activity of sympathetic nervous system and offer unique tool to monitor the level of beta-blockade in heart failure. The accurate diagnosis and stratification of the syndrome requires the combination of markers being specific for both organs such as BNP or NGAL.

Cardiac remodeling is the key feature of heart failure perpetuating the vicious cascade of heart failure progression. Candidate biomarkers include several novel inflammatory biomarkers such as galectin, growth differentiation factor (GDF) -15 or ST2 and interleukin 33. ST2 protein is involved in the regulation of inflammatory response in cardiac and non cardiac diseases suggesting multiple applications of this markers across the broad spectrum of diseases. We and others have shown elevated serum ST2 in patients with pressure overload hypertrophy and congestive or diastolic heart failure. Our data support diastolic load as a predominant hemodynamic factor that contributes to extra-myocardial production of ST2 in heart disease. Of not, our findings also indicate that overloaded myocardium is not a major source of circulating ST2. We showed that endothelial cells possess a functional ST2 secretory system in vitro, providing proof-of-concept for ST2 production by the vascular endothelium in vivo, which can be investigated in future studies (JACC2008). Elevated ST2 levels above 35 ng/mL are strongly associated with poor clinical outcome independently of BNP. In contrast to BNP, ST2 assessment is not clouded by age, renal function or body mass index. Similar to BNP monitoring, serial ST2 assessment is of incremental value in the prognostic stratification and monitoring of heart failure therapy. In particular, the combination of ST2 and BNP assessment in a multimarker strategy appears to have a complementary added value in predicting incremental risk for future clinical outcomes. Of interest is also the identification of interleukin 33 as nuclear factor regulating inflammation indicating its possible therapeutic potential in inflammatory diseases.

GDF-15 is not expressed in heart under normal physiological conditions but increases rapidly in response to cardiovascular injury, such as pressure overload, heart failure, ischemia/reperfusion, and atherosclerosis (5). Increased circulating levels of GDF-15 are linked to the onset and prognosis in heart failure. In some studies, the prognostic information provided by GDF-15 in these studies was independent of established clinical risk factors and biomarkers, including BNP, cardiac troponins, or CRP, indicating that GDF-15
provides insight into a distinct physiological process. Other observations suggest lower specificity of GDF-15 and advocate for its use in combination with other clinical factors and indicators.

Galecin-3 induces fibrosis, myofibroblast proliferation and tissue repair. The level of plasma galectin-3 is related to the changes of left ventricular structure and function, indicating that galectin-3 may have been involved in the process of left ventricular remodeling in CHF. It has been estimated that 30-50% of heart failure patients have an inherently progressive form of the disease mediated by high levels of Galectin-3. The broader adoption of Galectin-3 is hampered by its lower sensitivity and should be preferable used in the multimarker strategy, specifically in combination with NT-proBNP.

Progressive left ventricular dysfunction is also characterized by activation of the pleiotropic inflammatory cytokines. Several cytokines affect directly myocyte function and contribute to depressed cardiac contractility. On the other hand, number of them target extracellular matrix and cause degradation and remodelling of structural proteins supporting cardiac myocytes, thereby contributing to negative remodelling, eneffective cardiac mechanics and failure. Matrix metalloproteinases (MMPs) comprise several subgroups of proteases degrading matrix proteins and their serum activity correlates with various phenotypes of heart failure. The addition of MMPs to analyses of biomarkers may optimize the diagnosis and prognosis of heart failure by including distinct aspect pending the standardization of the collection and analysis techniques as well as appropriate referent age-matched references.

In summary, the advances in our understanding in pathophysiology of heart failure accelerated the introduction of biomarkers in the management of heart failure. Despite complexity of the syndrome, natriuretic peptides became benchmark biomarkers in heart failure. Other novel markers could help to pave our way and orient us better in the complexity of heart failure and its optimal management. Further progress is likely be accelerated by applying novel approaches such as proteomics where large platforms may lead to optimization of either existing proteins or identification of new proteins in a systemic standardized approach matched to the phenotype and acuteness of heart failure. Their validation in specific settings provides the required milestone to move beyond the benchmark biomarkers and address whether the multimarker analysis or personalized
approach may offer added value in both population- or patient-based management and truly open the era of “precision” medicine much as we witness in the oncological field.

References


4. **CLINICAL DOPPLER ECHOCARDIOGRAPHY IN DIAGNOSIS OF DIASTOLIC HEART FAILURE**

*Martin Penicka and Jozef Bartunek*

The prevalence of heart failure with preserved ejection fraction (HFPEF) is steadily increasing and its prognosis is poor (1-3). LV diastolic dysfunction, either alone or in combination with other factors (figure 4.1), is the major underlying mechanism of HFPEF (3-5). In the general population, the presence of even mild clinical diastolic dysfunction has been associated with increased all cause mortality (6) underscoring the critical importance of accurate diagnosis of underlying diastolic dysfunction.

**Figure 4.1**

*Causes of heart failure with preserved ejection fraction (HFPEF). Diastolic dysfunction is present in the majority of patients with HFPEF and thus it can be viewed as a marker of HFPEF. Diastolic dysfunction is a sensitive rather than a specific index of HFPEF. In other words, in the absence of diastolic dysfunction the diagnosis of HFPEF is less likely. Several studies have demonstrated a potential role of other cardiac and non-cardiac abnormalities in the pathogenesis of HFPEF. Of note, HFPEF is a disease associated with old age and therefore there is a high prevalence of other, non-cardiac, comorbidities (upper right corner). This makes the differential diagnosis of dyspnoea in the elderly quite challenging. COPD, chronic obstructive pulmonary disease; Hb, haemoglobin.*
The European Society of Cardiology guidelines define HFPEF as a clinical syndrome characterized by the presence of signs and symptoms of heart failure, preserved LV ejection fraction of a non-dilated left ventricle, and evidence of diastolic dysfunction (impaired LV relaxation or increased LV diastolic stiffness) with elevated LV filling pressures (3). LV diastolic dysfunction and filling pressures can be assessed non-invasively using Doppler echocardiography (7). Here, we address the role of Doppler echocardiography in the clinical diagnosis of HFPEF.

**Diagnosis of HFPEF can be easy.** In patients presenting with acute decompensated heart failure, the differential diagnosis of dyspnoea does not usually pose any significant problems. These patients have clear signs and symptoms of congestion, and elevated LV filling pressures and B-type natriuretic peptides as typically measured by BNP or N terminal pro-BNP (NT-proBNP) assays. Echocardiography usually shows a pseudonormal or restrictive transmitral flow pattern and, in cases with diastolic heart failure, a reduced peak early diastolic velocity of the mitral annulus longitudinal motion (e').

Discrimination between a normal and a pseudonormal transmitral flow pattern may sometimes represent a dilemma if the assessment of echocardiography findings is done in isolation without being directly involved with the patient's clinical management. Patients with the pseudonormal transmitral flow usually show clinical signs of heart failure. However, this is not the focus of this article.

The other ‘easy’ diagnostic group includes patients with inherited or acquired restrictive cardiomyopathy, and, less often, cases of hypertrophic cardiomyopathy. These patients have notably increased LV stiffness (a left and upward shift of the end-diastolic pressure–volume relationship) with a restrictive LV filling pattern (E/A ratio >2 along with a deceleration time <160 ms) and a low e'. Such patients, however, represent only 3% of subjects with HFPEF.

**Diagnosis of HFPEF can be difficult.** The differential diagnosis of HFPEF is challenging in stable elderly patients with equivocal symptoms. In contrast to younger, more active, individuals, symptomatology in the elderly is atypical or limited, partly also due to impaired mobility. These patients may report chronic moderate dyspnoea (New York Heart Association (NYHA) functional class II–III), fatigue or occasional palpitation, or they may simply report that they do not feel as usual or that something is wrong, but without a clear articulation of symptoms. These complaints are associated with a variety of diseases but
also with heart failure. In fact, the majority of patients with HFPEF are elderly individuals (mean age 75 years) clearly fulfilling the above mentioned characteristics (3, 6, 8). Since they do not show signs of congestion applying the European Society of Cardiology definition of HFPEF is questionable. Furthermore, these patients show subtle abnormalities in multiple indices of systolic and diastolic function, but without a single leading pathology (9). LV stiffness is only mildly to moderately increased. The resting LV filling pressures and NT-proBNP are normal or slightly elevated. Echocardiography shows an impaired relaxation transmitral flow pattern which is a non-specific finding in the elderly (figure 4.2). Finally, the high prevalence of non-cardiac comorbidities in this age group makes the differential diagnosis challenging (figure 4.1) (1, 2, 10). In clinical practice, many causes of moderate dyspnoea, without the presence of a significant pathology on routine examinations, remain unexplained or are attributed simply to deconditioning or being mildly overweight. Other patients, without a defined diagnosis, are administered thiazide-type diuretics. The complexity of this problem is illustrated in the following cases.

**Figure 4.2**

![Figure 4.2](image)

*Impaired relaxation transmitral flow pattern (E<A). In the elderly, this pattern can be associated with normal diastolic function, or preclinical diastolic dysfunction (isolated echocardiography abnormality) with low pressure left ventricular (LV) filling and the absence of heart failure with preserved ejection fraction (HFPEF), or clinical diastolic dysfunction leading to the increase in LV filling pressure and HFPEF. Thus, in elderly patients with a preserved LV ejection fraction, an impaired relaxation transmitral flow pattern is a non-specific finding which cannot be used alone to assess LV diastolic function. LAP, left atrial pressure.*
Case 1. A 72-year-old woman presented with chronic dyspnoea NYHA class II–III. Her history was noticeable for mild hypertension with normal blood pressure while on medication. Physical examination revealed bilateral perimalleolar oedema and normal jugular filling without hepatojugular reflux. Blood analysis showed mild anaemia (haemoglobin (Hb) 10.2 g/dl) and normal NT-proBNP (88 pg/ml). She was in sinus rhythm without reversible myocardial ischaemia during MIBI scintigraphy. Echocardiography showed borderline wall thickness with mildly increased LV mass (101 g/m²), normal LV ejection fraction of a non-dilated left ventricle, mildly enlarged left atrium (volume index 29 ml/m²), and borderline systolic pulmonary artery pressure (sPAP) (35 mm Hg). An impaired transmitral flow pattern suggestive of impaired relaxation was noted (figure 4.2). The question was posed whether the dyspnoea is of cardiac origin. Thus, whether the patient had HFPEF.

In the differential diagnosis of HFPEF, the following systematic approach should be applied (figure 4.3). The first step is to assess LV diastolic function. Impaired LV relaxation is a marker of HFPEF regardless of the underlying mechanism. If LV relaxation is normal, HFPEF is unlikely. In the population of ambulatory patients, who are older than 65 years and have normal LV ejection fraction, approximately 50% has normal age appropriate diastolic function while the majority of the remaining patients show a low e’ suggesting reduced LV relaxation (6, 11). If LV relaxation is reduced, the second step is to establish whether the degree of impairment has any clinical relevance for a patient. In other words, to evaluate whether the diastolic dysfunction leads to increased LV filling pressures during the individual’s daily routines and thus to symptoms of HFPEF. This may be very challenging because the low e’ may be associated either with a preclinical (asymptomatic, latent) diastolic dysfunction or with HFPEF (clinical diastolic dysfunction). The preclinical diastolic dysfunction is characterized by reduced LV relaxation at rest but preserved diastolic reserve to maintain normal LV filling pressures during the individual’s daily activities. Preclinical diastolic dysfunction causes no symptoms or congestion, and it portends a good prognosis. The majority of these patients will not develop HFPEF (12) In contrast, the clinical diastolic dysfunction is associated with reduced diastolic reserve and it leads to increased LV filling pressures and thus to HFPEF with a poor prognosis.
Stepwise approach to the diagnosis of heart failure with preserved ejection fraction (HFPEF) in elderly ambulatory patients with equivocal symptoms. Diastolic function is assessed using the average e'. If e' is preserved the classical form of HFPEF is not likely. In case of reduced e', the evidence of increased left ventricular (LV) filling pressures needs to be demonstrated. LV filling pressures can be assessed using the average E/e' ratio. A high E/e' confirms HFPEF. A low E/e' ratio is non-diagnostic and in such cases a multi-parametric strategy needs to be used. Sometimes, even after a complete non-invasive work up, a diagnosis still remains in doubt. In such cases, the direct assessment of LV filling pressure using heart catheterisation is advocated. However, it should be kept in mind that, in some patients, resting pressures may be normal. AP, angina pectoris; DT, deceleration time; IVRT, isovolumic relaxation time; LA, left atrial; MR, mitral regurgitation; NT proBNP, N terminal pro B-type natriuretic peptide; sPAP, systolic pulmonary artery pressure.

LV relaxation can be assessed using the average e’ from the septal and lateral corner of the mitral annulus (7). The recording of e’ is performed in the apical four chamber view using a pulsed wave tissue Doppler. The e’ cut-off values for different age groups were described in a recent set of recommendations (7). This particular patient had, with regard to her age, preserved myocardial relaxation (average e’ ≥9 cm/s) and the left atrium was only mildly dilated. Combination of the preserved e’ with either a normal or mildly dilated left atrium (left atrium volume index <34 ml/m²) defines normal LV diastolic function (7). Hence, her symptoms were not likely to be of cardiac origin (figure 4.4). Some less frequent causes of HFPEF should still be considered —for example, constrictive pericarditis, chronotropic
incompetence, dynamic mitral regurgitation (MR), severe dyssynchrony, and dyspnoea as an angina pectoris equivalent.

**Figure 4.4**

An impaired relaxation (E<A) transmitral flow pattern (left panel) with the corresponding pulsed wave tissue Doppler recording of longitudinal velocities from the lateral corner of the mitral annulus in the apical four-chamber view (right panel). In patients older than 60 years, impaired left ventricular (LV) relaxation is associated with a septal e’ <8 cm/s, lateral e’ <10 cm/s or average e’ <9 cm/s. In this case, the preserved e’ (septal e’=8 cm/s, lateral e’=11 cm/s, average e’=9.5 cm/s) indicates normal LV relaxation. This means that there is a high probability that heart failure with preserved ejection fraction can be excluded.

**Case 2.** A 67-year-old man with mild dyspnea presented with an impaired relaxation transmitral flow pattern and a low e’ suggesting impaired LV relaxation (figure 4.5). As it is known that older age is associated with reduced myocardial relaxation, question can be posed whether this findings reflect clinical diastolic dysfunction, ie a disease with a poor prognosis? Or is this a case of a preclinical benign diastolic dysfunction? The distinction between HFPEF and the isolated echocardiography abnormality is critical (7, 13).
Impaired relaxation transmitral flow pattern and low e’ in a male patient with mild dyspnoea. Of note, the left ventricular (LV) ejection fraction, LV mass, size of the left atrium (LA), and systolic pulmonary artery pressure (sPAP) were normal and the E/e’ ratio was in a non-diagnostic range compatible with both normal and increased LV filling pressures.

The clinical diastolic dysfunction is associated with permanent or intermittent increases in LV filling pressures leading to left atrial (LA) dilatation, atrial fibrillation, and elevation of sPAP. The ratio of transmitral flow E wave to e’ (E/e’) can be used to assess LV filling pressures. The E wave has been shown to have a positive correlation with preload and a negative correlation with LV relaxation. In contrast, e’ shows a stronger relationship with LV relaxation (14, 15). Hence, in patients with impaired myocardial relaxation and increased LV filling pressures (HFPEF, clinical diastolic dysfunction) the E wave increases and the e’ decreases. This leads to an elevation of the E/e’ ratio. Several studies have demonstrated a significant correlation between E/e’ and pulmonary capillary wedge pressure or LV end-diastolic pressure (4, 16). Yet, the accuracy of the E/e’ ratio to predict elevated LV filling pressures has been questioned as few studies reported a weak relationship between the e’ and LV relaxation (τ) (17–19). However, Kasner et al. (20) have addressed the relationship between invasive and noninvasive indices in the large invasive PV (pressure–volume) loop c
study including 43 HFPEF patients and 12 matched controls. In this study, the lateral e’-based indices (e’ <0.08 m/s, E/e’ ≥8, e’/a’ <1) showed high sensitivity and specificity to identify subjects with prolonged Tau, increased LV end-diastolic pressure, and LV stiffness. Assessment of the E/e’ is easy and highly feasible in most patients. Therefore, the joint guidelines of the European Association of Echocardiography and the American Society of Echocardiography recommend determining the E/e’ ratio as part of the assessment of LV filling pressures (7). The e’ and the E/e’ ratio should not be used in the presence of an extensive mitral annulus calcification, mitral stenosis, moderate to severe MR, surgical mitral rings and prosthetic valves. In patients with left bundle branch block, the septal e’ should be avoided. In patients with regional wall motion abnormality, the e’ from the adjacent mitral annulus corner should not be taken. Given these limitations, it needs to be emphasized that the e’ should be interpreted in the clinical context and in relation with other Doppler echocardiography indices. The detailed description of all the exceptions can be found in the guidelines (7).

High E/e’ ratio ≥13 (using average e’ from the septal and lateral mitral annulus) suggests increased LV filling pressures (LV end-diastolic pressure >16 mm Hg, mean capillary wedge pressure >12 mm Hg), while low E/e’ ≤8 usually indicates normal LV filling pressures. In patients with atrial fibrillation, the different cut off value (septal E/e’ ≥11) has been proposed to confirm increased LV filling pressures (7). Unfortunately, the majority of patients with HFPEF have an E/e’ in a non-diagnostic range (between 8–13) (16). This indicates the reduced sensitivity of the E/e’ ratio at rest to detect HFPEF. In such patients with a non-diagnostic E/e’ ratio, a multi-parametric strategy to assess LV filling pressure needs to be applied (figure 4.3). Prolonged isovolumic relaxation time (>100 ms) or very low E/A (<0.5) together with a long deceleration time (>240 ms) usually suggest normal LV filling pressures, except in cases of hypertrophic cardiomyopathy. In contrast, short isovolumic relaxation time (<60 ms) or high E/A (>2) along with a short deceleration time (<160 ms) and a low e’ are associated with increased LV filling pressures. LA volume reflects the cumulative burden and chronicity of elevated LV filling pressures. A biplane LA volume index ≥34 ml/m² is a strong predictor of an adverse outcome; hence, the use of this cut off has been recommended to distinguish between preclinical (isolated echocardiography abnormality) and prognostic (HFPEF) diastolic dysfunction (7, 21). As elevated LA pressure is usually associated with some degree of pulmonary hypertension, the presence of pulmonary
hypertension was shown to be a highly accurate indicator for distinguishing between HFPEF and controls (22).

Hence, in the clinical practice, many cases of ambulatory dyspnea are challenging because of borderline and controversial examination results despite employing the multiparametric approach recommended in the current guidelines. The resting E/e’ ratio and NT-proBNP are often in a non-diagnostic range. LA dilatation and pulmonary hypertension can be caused by conditions other than diastolic dysfunction (eg, arrhythmias, valvular diseases, lung disease, etc). Moreover, a significant proportion of patients with HFPEF have normal LV filling pressures at rest, with an increase only occurring during physical activity (23, 24). Therefore, diastolic stress echocardiography should be attempted whenever possible to unmask the diastolic reserve predisposing signs of diastolic heart failure. The reduced diastolic reserve in HFPEF is characterized by a failure to increase the rate of myocardial relaxation during exercise. Delayed myocardial relaxation cannot assure low pressure LV filling during increasing heart rates when diastolic filling time becomes shorter. This is illustrated in Figures 4.6 and 4.7, which show typical findings during diastolic stress echocardiography in patients with normal and reduced diastolic reserves, respectively. It is noteworthy that these two patients could not be correctly classified as having preclinical diastolic dysfunction or HFPEF using the recommended multi-parametric approach. In subjects with a normal relaxation reserve, exercise leads to an increase in both the transmitral flow E wave and the e’, and thus, the E/e’ ratio remains low. In contrast, in patients with an impaired LV relaxation reserve, a significant increase in the E wave is accompanied by only minimal augmentation of the e’, therefore the E/e’ ratio increases into the diagnostic range (Table 4.1).

**Table 4.1** Typical findings at diastolic stress echocardiography in patients with normal and impaired LV relaxation

<table>
<thead>
<tr>
<th></th>
<th>Normal LV relaxation</th>
<th>Impaired LV relaxation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmitral flow E</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>wave</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E’</td>
<td>↑</td>
<td>Slight ↑ ↔ ↓</td>
</tr>
<tr>
<td>E/e’</td>
<td>↔</td>
<td>↑*</td>
</tr>
<tr>
<td>DT E</td>
<td>Small ↓</td>
<td>↓ more than 50 ms†</td>
</tr>
<tr>
<td>sPAP</td>
<td>Minimal ↑</td>
<td>Significant ↑</td>
</tr>
</tbody>
</table>

I. *Cut off value for E/e’ not clearly defined (≥10–13).

J. †Depending on achieved heart rate.

DT, deceleration time; LV, left ventricular; sPAP, systolic pulmonary artery pressure.
Transmitral flow pattern and e’ at rest (left panel) and during submaximal bicycle exercise (right panel) in a patient with normal diastolic reserve. Of note, at submaximal exercise, e’ was normalized while E/e’ remained low, suggesting normal left ventricular filling pressures.
 Transmitral flow pattern and e’ at rest (left panel) and during submaximal bicycle exercise (right panel) in a patient with reduced diastolic reserve. Of note, at submaximal exercise, e’ remained low while the E/e’ ratio increased significantly, suggesting elevated left ventricular (LV) filling pressures.

The type and level of exercise used in stress echocardiography should be adjusted according to the patient’s daily routine and comorbidities. In younger, more active individuals, the preferred option is a tilting bicycle allowing continuous echocardiography monitoring. Indices of transmitral flow, e’ and the tricuspid regurgitation jet are recorded at rest and during submaximal exercise before the waves fuse (typically at heart rates between 100–120 beats/min). In older sedentary patients with limiting comorbidities or orthopedic problems, the performance of 10 sit-ups may represent a similar level of physical exercise as cycling for younger patients. Sit-ups are performed on the echocardiography table, so the recording of the transmitral flow and e’ can be done immediately after exercise. Some patients are unable to perform any sort of submaximal exercise. In these patients, a multi-parametric strategy should be employed to demonstrate structural or hemodynamic changes associated with periodic elevation of LV filling pressures (see below).
Table 4.2 shows the variables associated with normal and abnormal diastolic function. Patients with unequivocally normal diastolic function are characterized by preserved e’, a normal sized left atrium, and normal hemodynamics. In contrast, patients with clinical diastolic dysfunction have a reduced e’, a dilated left atrium and increased LV filling pressures. These represent patients with a poor prognosis. In clinical practice, the separation of patients with a normal versus an abnormal diastolic function (case 1) does not usually pose a problem. In contrast, in ambulatory patients presenting with dyspnoea and reduced e’, it is challenging to distinguish those with HFPEF from those with the isolated echocardiography abnormality. These patients often fall into the intermediate group (table 4.2) with reduced resting myocardial relaxation (e’) but without LV hypertrophy, LA dilatation or hemodynamic impairment (case 2). The majority of such patients will have normal diastolic reserve and no HFPEF. However, in some of them, the isolated diastolic dysfunction may deteriorate to HFPEF within 10 years (12). It is worth noting that in the patient in case 2, there was a significant increase in e’ during submaximal bicycle exercise, suggesting preserved diastolic reserve (figure 4.6). So it reasonable to conclude that, in this case, the reduced myocardial relaxation at rest has no structural, hemodynamic or prognostic impact on the patient. This is a case of the preclinical or isolated echocardiography abnormality.

Table 4.2 Doppler echocardiography characteristics and NT-proBNP in patients with E<A transmitral flow pattern, normal LV relaxation, preclinical (isolated echocardiography abnormality) and clinical (prognostic heart failure with preserved ejection fraction) diastolic dysfunction

<table>
<thead>
<tr>
<th>E&lt;A transmitral flow (&gt;60 years old)</th>
<th>Normal LV relaxation</th>
<th>Preclinical diastolic dysfunction</th>
<th>Clinical diastolic dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average e’ (cm/s)</td>
<td>≥9</td>
<td>&lt;9</td>
<td>&lt;9</td>
</tr>
<tr>
<td>LA volume index (ml/m²)</td>
<td>&lt;33</td>
<td>&lt;33</td>
<td>≥34</td>
</tr>
<tr>
<td>sPAP (mm Hg)</td>
<td>≤36</td>
<td>≤36</td>
<td>≥36</td>
</tr>
<tr>
<td>NT-proBNP (pg/ml)</td>
<td>&lt;220</td>
<td>&lt;220</td>
<td>&gt;220</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Average E/e’ rest/exercise</td>
<td>≤8</td>
<td>≤8</td>
<td>≥13</td>
</tr>
</tbody>
</table>

LA, left atrial; LV, left ventricular; NT-proBNP, N terminal pro B-type natriuretic peptide; sPAP, systolic pulmonary artery pressure.

Figure 4.8 shows two elderly patients with chronic dyspnoea. It is evident that both
patients have reduced myocardial relaxation but only one of them suffers from HFPEF. Of interest, despite a notably different prognosis, both patients are classified as stage I (mild, impaired relaxation pattern) diastolic dysfunction according to the current guidelines. The abnormality leading to HFPEF with increased mortality cannot be graded as mild. This example points out limitations of the currently used indices to assess LV diastolic function. This example also clearly demonstrates that TDI assessment of LV relaxation by e’ should not be used as the sole parameter to evaluate LV diastolic function. In contrast, LV relaxation (e’) should be interpreted in the context of LV and LA morphology, function, haemodynamics, and response to exercise.

**Figure 4.8**

Transmitral filling pattern, e’ and an invasive left ventricular (LV) end-diastolic pressure in two elderly patients with chronic dyspnoea, one with non-cardiac dyspnoea (A) and one with heart failure with preserved ejection fraction (HFPEF) (B). Both patients presented with an impaired relaxation transmitral flow pattern and low average e’. Despite similar echocardiography characteristics, only one patient showed increased LV end-diastolic pressure during left heart catheterisation. Thus, the left panel (A) shows an example of preclinical diastolic dysfunction (isolated echocardiography abnormality) while the right panel (B) shows an example of HFPEF (clinical diastolic dysfunction). Of note, according to the current guidelines, both patients would be classified as mild (stage I) diastolic dysfunction. EF, ejection fraction; NYHA, New York Heart Association functional class.
Practical approach to identify HFPEF. Figure 4.3 shows an integrated approach to confirm the diagnosis of HFPEF in stable elderly patients with preserved LV ejection fraction and chronic moderate dyspnea. In the minority of these individuals, the resting E/e’ ratio will be elevated (≥13) and the resting e’ will be reduced (≤9 cm/s). This suggests increased LV filling pressures in the setting of diastolic LV dysfunction, thus, HFPEF. Furthermore, these patients will likely show some degree of congestion during the physical examination accompanied by a pseudo-normal transmitral flow pattern. However, the vast majority of stable outpatients with dyspnoea will present with an impaired relaxation transmitral flow pattern, reduced e’ (<9 cm/s), but a low E/e’ ratio (<13) falling into the border zone based on the recommended multi-parametric strategy. These individuals could still have HFPEF that presents with either normal (E/e’≤8) or borderline (E/e’ 9–12) LV filling pressures at rest. In such patients exercise echocardiography should be attempted whenever possible. The type and level of exercise should be adjusted according to the patient’s daily routine and comorbidities. One of the advantages of using exercise is that the patient serves as his or her own control. This may reduce the confounding effects of various factors on the relationship between the e’ related indices and LV relaxation. In patients who are unable to exercise, a multi-parametric strategy should be employed (figure 4.3, table 4.2). Diagnostic accuracy improves with increasing numbers of positive markers.

Conclusion. The differential diagnosis of dyspnea in elderly, stable patients with normal LV ejection fraction is challenging. The majority of these individuals have no signs of congestion during the physical examination, while Doppler echocardiography shows an impaired relaxation transmitral flow pattern, reduced e’ and a low E/e’ ratio in a non-diagnostic range. To distinguish between the isolated echocardiography abnormality and the clinical diastolic dysfunction, LV relaxation (e’) should be interpreted in the context of LV and LA morphology, and hemodynamics. In the majority of patients, a multi-parametric strategy including diastolic stress echocardiography should be deployed to diagnose HFPEF. This stepwise approach should be further optimized to further increase the diagnostic accuracy.
References


5. **DYSSYNCHRONOUS HEART FAILURE: CELLULAR AND ELECTROPHYSIOLOGICAL SIGNATURE**

*Marc Vanderheyden and Jozef Bartunek*

Cardiac resynchronization therapy (CRT) is an established therapy for advanced heart failure in patients with conduction delay (1). The resynchronization of the mechanical coordination between left and right ventricles with reduction of the inefficient, out-of-phase contractions improves the mechanical efficiency of the chamber contraction-relaxation cycle leading to a better hemodynamic performance (2). Numerous randomized controlled trials demonstrated an improvement in symptoms and exercise tolerance in patients with congestive heart failure and cardiac dyssynchrony on top of optimal medical therapy which translated into better prognosis and improved survival (3-5). Favorable alterations of clinical course and outcome were consistent across the multiple studies and the therapy has become the Class I indication for advanced heart failure patients with broad QRS complex, severely depressed left ventricular function and sinus rhythm (1). To date cardiac resynchronization therapy remains the only treatment that enhances systolic function while improving long-term outcome and survival (2, 3, 6, 7). Furthermore, once dyssynchrony is ameliorated by CRT, patient outcome is better than in heart failure individuals with less dyssynchrony at the initial presentation (8). Here, we review the molecular alterations associated with dyssynchronous heart failure and their reversibility induced by cardiac resynchronization therapy.

**Dyssynchronous Heart Failure: A Distinct Phenotype**

The dyssynchronous contractions in heart failure patients with left bundle branch block morphology represent a specific disease entity, termed dyssynchronous heart failure (9). Besides typical ventricular dilatation and asymmetric hypertrophy, it is characterized by regional differences in loading and contractile work with differences in regional myocardial blood flow and oxygen consumption (10, 11). In dyssynchronous hearts, the workload is lowest in the septum and highest in the LV lateral wall associated by regional differences in the wall stress (12). Disparities in wall stiffening that generate dyssynchronous motion are most apparent in early systole during isovolumic contraction...
and late systole as one territory enters relaxation while the other is still contracting (12). In contrast to other forms of cardiomyopathy (11-13) the dyssynchronous phenotype of cardiomyopathy is characterized by regional differences in relative wall thickening with myocardial hypertrophy most pronounced in the late-activated lateral wall (10, 14). This results in mechanical inefficiency and functional mitral regurgitation caused by delay in the rise in LV intracavitary pressure (15) and by discoordinate papillary muscle contraction (16). Effects of abnormal electrical activation on left ventricular pump function are independent of loading conditions and present at rest as well as during (17). Overall, cardiac dyssynchrony is associated with reduced mechanical output and efficiency.

**Electrical vs Mechanical Dyssynchrony**

In order to understand the pathophysiological mechanisms governing dyssynchrony in heart failure, one need to recognize that structurally normal hearts exhibit also some degree of non-uniformity. This is related to complex myocardial spatial and geometric architecture given by the opposite myocardial fiber orientations. As such, it is not surprising that myocardial regions must be electrically activated timely for efficient pump function.

It should be noted that electrical and mechanical dyssynchrony are not synonymous. Although conduction defects are common, they do not always result in the mechanical dyssynchrony. On the other hand, 30-50% of patients with heart failure in absence of regionally delayed electrical activation with a narrow QRS complex can exhibit mechanical dyssynchrony regardless the degree of left ventricular dysfunction (18-20).

Experimental data demonstrate improvement in ventricular hemodynamics with CRT despite any change in electrical dyssynchrony (21). At detailed electro-mechanical mapping of dyssynchronous hearts, the electrical map shows early right heart stimulation rapidly moving to the lateral free wall whereas the mechanical map will follow a similar pattern of contraction but typically with a slower spread (17, 22, 23). In contrast to electrical dyssynchrony where the primary activation delay is typically manifested by a widened QRS complex, the transformation of electrical into mechanical dyssynchrony is complex. This is because mechanical dyssynchrony is not triggered only by excitation of the tissue but also by myofilament calcium cycling and responsiveness, regional loading or regional differences in myocardial fibrosis (Figure 5.1). In this regard, it should be also noted that altered loading conditions in heart failure can contribute to dyssynchrony. This is important for the
interventional decision because dyssynchrony caused by electrical delay can be targeted by CRT, whereas that caused purely by regional properties and/or loading disparities may not.

**Dyssynchronous Heart Failure: The Molecular signature**

In addition to differences in the chamber mechanics and remodeling, dyssynchronous heart failure is associated with a distinct molecular signature in addition to global changes typically seen in the failing myocardium (Figure 5.1). In addition to activation of the fetal gene program, changes in betadrenergic signaling or energetics, dyssynchronous heart failure is also characterized by activation of apoptotic cell death. (24, 25) Apart from global changes in transcriptional fingerprint, regional differences in gene expression were documented in dyssynchronous heart failure (26, 27). The molecular heterogeneity is characterized by upregulation of numerous myocardial transcripts or proteins between the early (anterior) and late-activated (lateral) regions including calcium handling proteins, proteins involved in metabolic pathways, extracellular matrix remodeling and myocardial stress responses (13, 14, 26, 27). Though human data are scarce, they are in line with the experimental observations. Initial insights upon the effects of CRT on the molecular portrait of dyssynchronous heart failure in humans were provided by D’Ascia et al. who demonstrated a reduction in interstitial myocardial collagen volume, tumor necrosis factor-α levels and apoptosis following CRT (25).

Note, CRT can reserve altered myocardial gene expression in the clinical setting (28, 29). In patients treated with the therapy, a significant upregulation of gene expressions of the Ca$^{2+}$ handling proteins sarcoplasmic reticulum calcium ATPase 2α (SERCA), phospholamban (PLN) as well as a significant increase in the ratio of SERCA to PLN (Figure 5.2) and in the ratio of SERCA to the sarcolemmal sodium calcium exchanger (38) has been noted. Clinical response to the therapy was associated with a correction of the isoform switching of the contractile genes with an upregulation of the fast α-myosin heavy chain and an increase of the α-myosin to β-myosin heavy chain mRNA ratio (28). Thus, beneficial effects of CRT on LV function and remodeling in human heart failure are associated with “reversed” molecular remodeling. However, they should be interpreted with caution since careful examination of the heterogeneous gene expression in humans is hampered due to the inability to biopsy from different regions.

44
Figure 5.1

Molecular signature of dyssynchronous heart failure is associated with global changes typical for molecular signatures in heart failure as well as with the distinct regional heterogeneity in the cardiac molecular signature related to mechanical dyssynchrony. ECM indicates extracellular matrix; RGS: regulators of G-protein signaling.

Dyssynchronous heart failure: Electrophysiological abnormalities

The electrophysiological hallmark of failing heart is prolongation of action potential duration. However, in parallel with distinct molecular signature, the dyssynchronous failing heart is also characterized by additional distinct electrophysiological abnormalities (30-32). Conduction velocities and repolarization times are markedly altered in the late-activated regions especially at the endocardial levels and the action potential duration in the late-activated regions is reduced. This creates a highly arrhythmogenic substrate with frequent early afterdepolarisations (EAD). CRT dramatically reduces the frequency of EADs by reducing the LV regional heterogeneity in action potential duration (31).

At the molecular level, the reduced intraventricular conduction has been attributed to a downregulation and redistribution of the gap junction protein connexin-43 (Cx43) from its usual location at the intercalated disk to the lateral sarcolemma (30, 32). In addition,
regional differences in ionic Na\textsubscript{+}, K\textsuperscript{+} currents and Ca\textsuperscript{2+} transients were observed between myocytes isolated from the anterior and lateral LV myocardium in parallel to overall blunted β-adrenergic signaling and modulation of ionic currents is blunted in (33, 34).

CRT partially reverses the dyssynchrony-induced down regulation of K\textsuperscript{+} current and improves Na\textsuperscript{+} channel gating and Ca\textsuperscript{2+} homeostasis in myocytes from delayed myocardial segments (35). It also normalizes APD in the lateral myocytes and reduces the LV regional gradient of APD, thereby suppressing the development of EADs (35). Taken together, these findings provide mechanistic understanding of increased arrhythmogenic susceptibility in patients with dyssynchronous heart failure. Although hypothetical, partial normalization of the electrical phenotype by CRT may also explain improved prognosis and reduced arrhythmogenic risk after CRT (33, 35).

**Resynchronization and its effects on adrenergic responsiveness and mechano-energetics**

The control of cardiac function starts at the level of the myofilament level where calcium-interactions with regulatory thin-filaments determine the net generated force. The Kass group (35) described post-translational defect in regulatory myofilament proteins in cardiac dyssynchrony. This was corrected by resynchronization without increased energy demand, an effect that can be consistent with effects of “myofilament sensitizers”.

One of the clinical hallmarks of heart failure is the occurrence of exercise intolerance. Reduced β\textsubscript{1}-adrenergic receptor abundance, increased receptor phosphorylation triggering receptor desensitization and internalization, enhanced Gi-coupled signaling linked to PKA phosphorylation of β\textsubscript{2}-AR, and depressed adenylate cyclase activity account at least partially for this observation (35). They induce chronotropic impairment and reduce the myocardial contractility reserve with a blunted force frequency response (28). Our clinical studies demonstrated that CRT improves this blunted force-frequency relationship (Figure 5.2) and amplifies the contractile reserve in response to inotropic stimulation (28, 36) attributable to increased expression of β1-adrenergic receptors without any change in β2-adrenergic receptors (28).
Force-frequency relationship at baseline (AAI pacing) and at follow-up, 3 months after CRT. Upper left panel indicates SERCA myocardial gene expression at baseline and at follow-up, 3 months after cardiac resynchronization pattern. Upper right panel indicates Phospholamban (PLN) myocardial gene expression before (baseline) and at follow-up, 3 months after cardiac resynchronization therapy. Lower left panel indicates the ratio of SERCA/PLN before (baseline) and at follow-up, 3 months after cardiac resynchronization therapy. Lower right panel indicates force-frequency relationship (FFR) before, during AAI pacing (straight line) and at follow-up during biventricular pacing (dotted line). * indicates p < 0.05 compared to similar heart rate AAI vs CRT. ** indicates p < 0.05 compared to baseline.

Chakir et al. (37) extended these human data by demonstrating that these changes occur globally both in early and late activated myocytes. Apart from up regulation of the β1-adrenergic receptors, as the basic mechanism related to improvement in adenylate cyclase activity, they provided novel insights by reporting up regulation of regulators of G-protein signaling (RGS) proteins (38) (Figure 5.3). RGS proteins appear to negatively regulate G-protein coupled signaling by acting as GTPase accelerators. In particular, improved adrenergic reserve was associated with RGS2 and 3 upregulation. The upregulation of these modifying proteins was directly related to changes in Gαs-biased β2-AR signaling that enhances cAMP activation and stimulation of PKA within the SR, thereby improving cell Ca^{2+}
cycling and contraction. It is of note that enhanced RGS2 and RGS3 expression was found in humans responsive to CRT but absent in nonresponders (38).

Figure 5.3

**β-adrenergic receptors (AR) and G-receptor coupled signaling: CRT upregulates regulators of the G protein signaling (RGS).** $\beta_1$-AR indicates $\beta1$ receptor, $\beta_2$ indicates beta 2 receptor, $\alpha_s$: $\alpha$ subunit with stimulatory effect of the GTP-binding protein, $\alpha_i$: $\alpha$ subunit with inhibitory effect of the GTP-binding protein, RGS regulators of G-protein signaling (RGS) proteins and CRT cardiac resynchronization therapy.

Such molecular changes have not been described in any previous medical or interventional therapeutic strategies in congestive heart failure and appear to be a unique feature of resynchronization intervention in dyssynchronous heart failure (38).

While other heart failure therapies target a specific neurohumoral factor or profoundly unload the left ventricle to improve $\beta$-adrenergic responsiveness, CRT is able to achieve the same effect without any excessive catecholamine stimulation. In agreement with this, Nelson et al. showed that resynchronization increases LV $\mathrm{dP/dt}_{\text{max}}$ while even slightly decreasing myocardial oxygen consumption (2). This restoration of the normal balance between catecholamine stimulation and myocyte adrenergic responsiveness without any increase in catecholamine content is remarkable in comparison to other therapeutic interventions in congestive heart failure. It has been attributed to a rapid instantaneous effect, resulting from the re-timing of contraction to occur synchronously in
both sides of the myocardium, thereby reducing wasted chamber work and improved compromised mechano-energetics. This phenotypic effect is related to improved cellular energy metabolism and improved mitochondrial function (39). Hence, similar to the electrical and adrenergic remodeling, these data support the notion that in addition to enhancing mechanical efficiency at a chamber level, the beneficial effects of CRT could be related to changes in the cellular energy metabolism in the mitochondria.

**Clinical Implications**

What take-home messages can clinicians and scientists take from translational data on dyssynchronous heart failure? One obvious message is that a detailed analysis of the “global or regional” mechanics and electrophysiological aspects of dyssynchronous heart failure with zeroing on molecular portraits is able to unravel the fundamentals of the disease and its reversibility. Dyssynchronous heart failure is characterized by global as well as regional cellular and molecular changes, which are not observed in synchronous heart failure. The beneficial effects of CRT on myofilament function, G-coupled signaling and adrenergic response, are important components for restoring cardiac reserve and reducing arrhythmia risk. Accumulated evidence suggests that CRT is a unique therapeutic intervention capable of restoring cardiac function without increasing energy demand. Yet, despite overall survival benefit, 30% of candidate patients remain non-responders to the therapy. Bioinformatics, proteomics and genomics hold the potential to further unravel comprehensive molecular networks underlying the benefits of the CRT and how to optimally employ this therapy. It is noteworthy, that responders and non-responders are characterized by differences in baseline gene expression profiles despite similar baseline hemodynamic derangement suggesting that “molecular profiling” with utilization of the proteomic or genomic platform can facilitate further optimization of the patient stratification. The features of dyssynchronous heart failure and its reversibility offer also a unique opportunity to decipher more general biomarkers and therapeutic targets and may help to further advance the population-based as well as individualized, “precision-based” treatment of all-around patients presenting with congestive heart failure.
References


6. **TAILORED APPROACH TO FUNCTIONAL MITRAL REGURGITATION IN HEART FAILURE**

*Martin Penicka and Jozef Bartunek*

Functional (ischemic or non-ischemic) mitral regurgitation (MR) is highly prevalent in patients with systolic heart failure and its presence is associated with worse long-term survival, independently of other baseline characteristics and degree of LV dysfunction. Several studies have reported that 30% of patients with chronic systolic heart failure had echocardiography evidence of moderate-to-severe (grades 3/4 and 4/4) MR. The presence of significant MR is an independent predictor of survival regardless of etiology of the heart failure, degree of left ventricular (LV) dilation or ejection fraction. Patients with moderate to severe MR show a twofold increase in mortality and a fourfold increase in hospitalizations for worsening heart failure. Less severe MR (grades 2/4 and 2+/4, effective regurgitant orifice between 20-30 mm²) has also been associated with reduced survival. This suggests that even moderate MR should receive attention and therapeutic consideration. It is surprising and disappointing that despite the ominous prognosis associated with MR in heart failure, there are almost no randomized trials described in the literature. The published evidence consists of single-center, observational, often retrospective, and at best, propensity matched studies. Therefore, therapeutic recommendations are based mostly on personal experience, expert consensus or pathophysiologic insights into the mechanism of functional MR; hence, it is challenging to provide evidence-based therapeutic guidance. This chapter will focus on an individually tailored approach to therapeutic management of functional MR in chronic systolic heart failure.

**Causal therapy of functional MR: pathophysiology based approach.** The most important mechanism of functional MR is LV remodeling. LV dilatation with increased sphericity or more localized post-infarction remodeling leads to a displacement of papillary muscles. This causes stretching of the chordae which leads to redistribution and increase of tethering forces, resulting in incomplete leaflet coaptation and MR. Mitral annulus-related factors and closing forces play a lesser role (Figure 6.1).
Functional MR (Carpentier type IIIb) is a valvular dysfunction secondary to myocardial disease. An imbalance between closing and tethering forces is the underlying mechanism of the disorder.

Figure 6.2 shows the typical echocardiography appearance of a mitral valve in functional MR, which is characterized by restricted systolic leaflet motion (Carpentier type IIIb) and tenting of the anterior leaflet. Functional MR is a complication of systolic heart failure resulting from LV remodeling. Onset of MR induces a vicious circle; MR leads to LV volume overload, which then leads to LV remodeling, which in turn leads to MR. Chronic volume overload is associated with structural and functional alterations of cardiomyocytes and the extracellular matrix. Within a time frame of months to years, these changes progress to an irreversible stage characterized by loss of cardiomyocytes and ‘replacement’ fibrosis. This suggests that causal therapy for functional MR should be targeted toward reverse LV remodeling; additionally, the treatment should be delivered promptly, before progression to an irreversible stage. Reverse LV remodeling is associated not only with decreased MR but also with a reduction of heart failure hospitalizations and improved survival. Figure 6.3 shows an overview of therapeutic interventions associated with reverse LV remodeling in systolic heart failure.
Figure 6.2

An example of a typical echocardiography appearance of a normal mitral valve (2A) and distorted mitral valve geometry leading to functional MR (2B). In healthy individuals with a normal left ventricle (2A), mitral valve leaflets are “flat” with the coaptation point (arrow) almost at the level of the mitral annulus (MA) plane. In contrast, in a dilated LV with functional MR (2B), the leaflets are pulled toward the LV apex due to the stretching of chordae, which results in tenting of the anterior leaflet and restrictive systolic motion of the posterior leaflet with the coaptation point (arrow) displaced apically and posterolaterally.
LA = left atrium, LV = left ventricle, MA = mitral annulus

Figure 6.3

An overview of therapeutic interventions associated with reverse LV remodeling in systolic heart failure. The left side of the panel shows treatable components of systolic heart failure, which should be promptly identified and treated. The right side of the panel shows acute mortality risk associated with each therapeutic intervention.
**Pharmacological therapy.** The first step is to optimize heart failure medication including beta blockers, ACE inhibitors or ATR blockers, and aldosterone blockers; the importance of this step should not be underestimated. Unless contraindicated, every patient with systolic LV dysfunction, regardless of the presence of MR, should receive the maximal tolerated dosage of these drugs with a target resting heart rate of 60 bpm, a systolic blood pressure of 110 mmHg and a NT-proBNP less than 1000 pg/ml. Optimal heart failure therapy has been shown to improve prognosis and reduce heart failure hospitalizations. Moreover, in selected patients, significant reverse LV remodeling has been demonstrated with MR reductions of 1-2 echocardiography grades, on average 10-15. It is noteworthy, that on an individual basis, the prediction of response to pharmacological therapy is challenging and many patients continue to have moderate or severe MR even after optimization of medication 15, 16. Favorable effects can be expected mostly in patients with of the large extent of myocardial viability, without extensive LV remodeling, and in the absence of significant dyssynchrony 17-19. The response to therapy should be evaluated after three months. Table 6.1 shows clinical and echocardiography characteristics of favorable responses, as well as therapy failure. Those who respond to therapy should be ambulatory, in NYHA class I or II, without signs of fluid retention, have low NT-proBNP and normal biventricular filling pressures (impaired relaxation transmitral flow pattern, normal systolic pulmonary artery pressure and preserved respiratory variation of inferior vena cava diameter). Furthermore, echocardiography needs to demonstrate both reverse LV remodeling (reduction in LV diameters, volumes and increased ejection fraction) and decreased MR down to the level of mild to moderate. It should be noted that stabilization of LV remodeling alone, without actual improvement, should not be viewed as successful therapy. Reduction of MR needs to be seen both at rest and during appropriate exercise levels, which reflect the daily routines of individual patients. Decreased MR at rest, with a huge increase during low-level exercise, should be regarded as treatment failure. In non-responders, other suitable therapeutic options should be considered, even at the expense of increased intervention-related risks.

**Cardiac resynchronization therapy (CRT).** In advanced systolic heart failure, LV dyssynchrony is very prevalent and its onset is associated with functional deterioration and a poor prognosis 20-22. LV dyssynchrony globally, but specifically between papillary muscles, has been shown to be a very important contributory mechanism of functional MR 23-25. Correction of LV dyssynchrony, by CRT, has been associated with improved survival
paralleled by reverse LV remodeling and reduction of MR \(^{18, 25-28}\). Several studies have demonstrated that reverse LV remodeling and resynchronization of contraction of papillary muscles are the main mechanisms underlying improvement in MR following CRT \(^{23-25, 27-29}\). On average, a decrease in MR by 1-2 echocardiography degrees can be expected \(^{30-32}\). A significant reduction of MR, at rest, has been observed immediately after CRT, and is attributed to resynchronization of the left ventricle and papillary muscles, with an acute recruitment of LV contractility and thus, an increase in closing forces acting on the mitral valve \(^{25, 28, 29, 33}\). In our study, despite a significant decrease in MR at rest, CRT failed to attenuate immediate exercise-induced MR \(^{28}\). During a three month follow up, CRT was shown to lead to a significant reverse LV remodeling paralleled by a further reduction in MR at rest, as well as by a significant attenuation of exercise-induced MR (Figure 6.4). Hence, the late, exercise-induced, reduction of MR and its dynamic component is strongly related to reverse LV remodeling \(^{28, 31, 33}\). It is worth noting that the amount of MR decrease correlates with the extent of reverse remodeling and an improved prognosis during mid-term follow up \(^{33}\). In contrast, persistent moderate (or greater) MR several months after CRT has been shown to be predictive of poor outcomes \(^{33}\). So it seems that an acute decrease in MR leads to reverse LV remodeling, which in turn leads to late decreases in MR. Furthermore, patients likely to experience beneficial effects are those individuals with significant myocardial viability and dyssynchrony \(^{18, 24, 28, 34}\). Effects of CRT should be evaluated within 3 months. In non-responders (Table 6.1), the optimization of pharmacological therapy and CRT (AV and VV delay) can be attempted with a complete re-assessment after another 3 months. Alternatively, there should be a timely consideration of other suitable therapeutic methods, such as mitral valve repair.
The potential mechanisms responsible for reduction of MR after CRT. Dyssynchronous activation of the papillary muscles and a more spherical ventricle with mitral valve leaflets tethering and tenting, all contribute to MR. In the acute phase post-CRT implantation, MR is reduced thanks to resynchronization whereas in the chronic phase, not only resynchronization but also reverse LV remodeling contributes to the improvement in MR. From ref 28.

Transcatheter mitral valve repair using MitraClip. Outcome of pharmacological therapy with or without CRT often remains unsatisfactory with many non-responders. Functional MR has been shown to persist in 20% to 25% of CRT patients and, in an additional 10% to 15% may actually get worse after CRT\(^2\). Therefore, other therapeutic modalities need to be considered. Transcatheter implantation of a MitraClip device (Abbot, USA) has recently emerged as a valuable, alternative, MR treatment. The MitraClip approach is based on the ‘edge-to-edge’ concept developed by Alfieri \(^{35}\). The technique involves grasping the free edges of the A2-P2 parts of the leaflets, thus creating a double orifice mitral valve, without causing mitral stenosis (Figure 6.5). The MitraClip is implanted using the femoral vein and a trans-septal puncture under general anesthesia and TEE and fluoroscopy guidance. In the EVEREST II (Endovascular Valve Edge-to-Edge Repair Study), a total of 279 patients with moderate to severe MR and suitable anatomy were randomized in a 2:1 ratio into MitraClip
or mitral valve surgery\textsuperscript{36}. Despite a lower efficiency in reducing MR, the MitraClip was associated with clinical outcomes similar to mitral valve surgery. It is noteworthy that in the EVEREST trial, 73\% of patients had degenerative MR\textsuperscript{36}.

Other studies have investigated MitraClip therapy in patients with severe systolic heart failure and significant functional MR (≥2/4)\textsuperscript{37,38}. MitraClip implantation was shown to be feasible and safe with a 30-day mortality between 4\% and 6\% in patients with prohibitive risk for mitral valve surgery\textsuperscript{37-39}. During a follow-up of 6 to 12 months, the MitraClip was associated with a reduction of MR, an improvement of NYHA class and significant reverse LV remodeling\textsuperscript{37,38}. The average reduction of MR achieved by MitraClip was 2 echocardiography grades, which left the majority of patients with mild to moderate residual MR (grades 1+/4, 2/4). This confirms the lower efficiency of MitraClip to reduce MR compared to surgical mitral valve annuloplasty, where the residual 2/4 grade MR is considered to be an unacceptable result. Nevertheless, these studies suggest, that even moderate reduction of MR is sufficient to induce significant reverse LV remodeling, which in turn leads to reduction of MR with favorable clinical outcomes. Of note, in around 50\% of patients, implantation of two clips during the same procedure was necessary to achieve the desired effect on MR\textsuperscript{37}. This is not surprising given the high prevalence of a large oval-shaped regurgitant orifice in many patients. Based on these results, it is tempting to speculate that MitraClip therapy is associated with a decrease in the predominantly dynamic component of functional MR. Along these lines, MitraClip can prevent the enlargement of the effective regurgitant orifice during increased hemodynamic load or physical activity, and thus, it stabilizes MR at mild to moderate degrees. In other words, after implantation of MitraClip, at rest, MR may appear the same as before, however, it has lost whatever dynamic component was present, which prevents progression towards worsening heart failure that might otherwise have taken place.

Taken together, the data from several studies suggest that the implantation of MitraClip could be safely performed in patients who failed to response to pharmacological therapy and/or CRT, have moderate-to-severe residual MR, suitable mitral valve anatomy, and a prohibitive surgical risk.
**Figure 6.5**

Example of the implantation of the MitraClip device. Left panel shows the positioning of the device at the site of the origin of the valvular regurgitation between P2 and A2 scallops of the mitral valve. Right panel shows the 3D image of a double orifice mitral valve after MitraClip implantation.

**Myocardial revascularization and impact on functional mitral regurgitation.** Myocardial revascularization, in the form of percutaneous coronary intervention (PCI), does not improve the natural history of moderate to severe functional MR. This was demonstrated by Pastorius, who examined long-term outcomes in 711 patients who had undergone PCI. On the other hand, surgical myocardial revascularization (CABG) seems to be more promising. In a recent large randomized trial (STICH) and many observational studies, CABG, when compared to pharmacological therapy, has been associated with reduced cardiovascular mortality and decreased hospitalizations for heart failure. The greatest benefit of CABG has been observed in patients with less extensive pre-CABG LV remodeling and a low-degree dyssynchrony. It is worth noting that several studies have demonstrated a close association between regression of functional MR post-CABG and reverse LV remodeling, suggesting the critical role of myocardial viability. We recently investigated preoperative predictors of unrepaired moderate (grades 2/4 and 2+/4) functional MR improvement in 121 patients with ischemic LV dysfunction (ejection fraction 35 ± 10%) undergoing isolated CABG. MR was assessed pre-CABG and at 12 months post-CABG. This study has demonstrated that greater myocardium viability and the absence of dyssynchrony between papillary muscles were the main independent predictors of long-term MR improvement after isolated CABG. Reduced MR was paralleled by reverse LV remodeling and associated with improved mitral valve geometry. This confirms that LV
functional recovery of viable myocardium is necessary to reduce tethering forces, increase closing forces and subsequent restoration of mitral valve function. Of note, extensive LV dilation prior to CABG and persistent high-degree dyssynchrony post-CABG do not allow viable myocardium to recover contractile function and reverse LV remodeling fails to occur despite revascularization \(^{17,18}\).

Several authors have also observed that factors, other than global LV factors, play an important, independent, role in the development of functional MR. For example, local LV remodeling with apical and posterior displacement of papillary muscles has been shown to be a major determinant of the degree of MR, and is independent of global LV dilation \(^{47-51}\). In corroborating these findings, our study showed that the degree of viability and absence of dyssynchrony in the segments adjacent to papillary muscles are also very important factors associated with reduction of functional MR after CABG \(^{24}\). The likely explanation is local reverse LV remodeling that ameliorates displacement of papillary muscles and reduces the mitral valve tenting area, along with synchronous contraction of papillary muscles with increased closing forces. Other authors have shown that the extent of mitral valve deformation significantly contributes to the severity of functional MR \(^{52-55}\). In non-ischemic dilated cardiomyopathy, the mitral valve tenting area has been shown to be strongly correlated with the degree of MR, functional status and plasma BNP \(^{52}\). Moreover, tenting area has been also independently associated with mortality and hospitalizations \(^{52}\).

This suggests that pre-CABG assessment of LV dilation, segmental viability and dyssynchrony, and mitral valve geometry may provide guidance as to whether or not to perform concomitant mitral valve annuloplasty in patients with systolic heart failure undergoing CABG.

**Mitral valve surgery.** In the majority of patients with functional MR, valve repair is associated with lower peri-operative mortality compared to valve replacement \(^{56-58}\). Restrictive mitral valve annuloplasty (MVA), using an undersized rigid ring, is therefore superior to valve replacement and it should be chosen whenever possible \(^{59}\). Restrictive MVA is an effective approach to reduce functional MR. However, there have been no randomized trials, to date, which compare survival benefits of MVA to pharmacological therapy or myocardial revascularization alone. There are several reasons for the lack of randomized trials; a major reason is probably a general reluctance of cardiac surgeons to take part in randomized trials, which likely stems from their view of each mitral valve
surgery as an individual work of art, which cannot be reproduced or easily compared to that of other surgeons-artists. Additionally, the disclosure of individual successes as well as peri-operative mortality rates, may represent a considerable obstacle to any inter-institutional comparisons. So, it is not surprising, that the first randomized trial in mitral valve repair was performed by cardiologists using percutaneous approaches.

Therefore, all the available evidence on effects of MVA have come from observational and propensity-matched studies. Based on these studies, several conclusions can be drawn. Functional MR is highly prevalent in patients undergoing CABG and its presence is associated with worse long-term survival, which is independent of other baseline characteristics and degree of LV dysfunction. While severe MR is not usually improved by revascularization alone, changes in cases of moderate MR, in response to revascularization, are highly variable. Patients with unrepaired even moderate MR have greater early and long-term mortality than similar patients without MR. Likewise, many patients show progression of MR during follow-up, despite revascularization. Hence, one might presume that, in patients with moderate to severe functional MR, mitral valve repair combined with CABG would offer an improved prognosis. However, several recent studies have failed to demonstrate a long-term survival benefit of combined procedures compared to CABG alone.

In a propensity matched analysis, Mihaljevic compared the effects of CABG plus MVA (n = 290) to isolated CABG (n = 100) in patients with moderate to severe (3/4, 4/4) functional MR. At one year follow-up, the CABG plus MVA strategy showed a lower prevalence of residual severe MR than CABG alone (12% vs. 48%). Despite these favorable effects on MR, concomitant MVA was not associated with an improvement in NYHA functional class or survival during a 10-year follow up. One of the potential explanations of these surprising findings may be that the state-of-the-art downsized rigid annuloplasty ring was used in less than 30% of patients. Furthermore, the failure of MVA to improve survival could also be attributed to the high recurrence rate of MR despite initially successful repair and higher peri-operative mortality of combined procedures compared to CABG alone. Braun et al. reported restrictive MVA outcomes in 100 patients with functional MR undergoing CABG. The authors systematically used downsizing of two ring sizes in order to achieve a coaptation height of at least 8 mm. The 30-day mortality was 8%. At 4.3 years of follow-up, restrictive MVA was associated with symptomatic improvement,
reverse LV remodeling, low MR recurrence (15%) and mortality (18%) rates. It is noteworthy, that these favorable results were observed only in patients with pre-operative less extensive LV remodeling (LV end-diastolic diameter ≤ 65 mm). Keeping with this line, De Bonis and Kang showed that MR recurrence, after repair, parallels the absence of reverse LV remodeling, and hence, the absence of myocardial viability. In 54 patients with severe MR and LV dysfunction undergoing CABG with MVA, the presence of myocardial viability (more than 5 segments) was associated with a long-term survival benefits. As previously shown, extensive LV dilation prior to CABG and persistent high-degree dyssynchrony post-CABG may hinder reverse LV remodeling and thus, the durability of MVA. This underscores the importance of myocardium-related factors such as viability, dyssynchrony and remodeling as outcome predictors for MVA. Apart from global LV-related factors, patients with severely distorted mitral valve geometry pre-MVA are likely to experience recurrent MR after successful MVA with a negative impact on 3-year survival. A subanalysis of the Acorn clinical trial, in 102 patients with non-ischemic dilated cardiomyopathy (mean LV ejection fraction 24%, LV end-diastolic diameter 70 mm) and severe functional MR, showed very promising results for undersized MVA. The peri-operative mortality was 1.6% and the 3-year mortality was 27%. Furthermore, restrictive MVA was associated with sustained reverse LV remodeling and a low recurrence of MR. Taken together, these studies suggest that a failing LV will benefit from relief of chronic volume overload imposed by severe MR. MVA can be performed safely with low peri-operative mortality. Moreover, MVA is associated with long-term reverse LV remodeling and low MR recurrence rates. The critical issue is the selection of suitable candidates.

Tailored approach to functional MR. The selection, sequence and amount of intervention should be tailored according to individual characteristics of the patient (Figure 6.3). It is important to realize that the majority of patients with chronic systolic heart failure are high-risk elderly who commonly have other cardiac comorbidities and may present after having undergone repeated percutaneous or surgical myocardial revascularizations. Hence, the logical approach is to begin with less risky procedures (optimizing pharmacological therapy plus selective CRT). If the primary treatment fails to meet the desired outcome, only then would it be time to move on to interventions associated with higher mortality risks (Figure 6.3, right side). LV dyssynchrony is a deadly, but treatable, complication of systolic heart failure. Because of that, every suitable patient should undergo implantation of a CRT-
D early in the disease course. Moreover, the presence of CRT often allows further up-titration of dosages of heart failure medication, which increases the chances of a favorable response. Optimizing pharmacological therapy, plus or minus CRT, is a safe initial strategy, which is also frequently effective and sufficient to improve LV remodeling, MR and the patient’s prognosis. Responders are mostly patients with less advanced heart failure with little elapsed time from the first diagnosis, non-ischemic cardiomyopathy, less extensive LV remodeling and significant myocardial viability. Response to therapy should be evaluated as early as 3 months (Table 6.1). In the absence of reverse LV remodeling and a reduction of MR, the therapy should be intensified or other therapeutic modalities should be considered, taking into account the severity of the underlying heart failure and peri-operative risk (Figure 6.3).

Patients with advanced “terminal” heart failure are usually beyond the horizon for mitral valve repair. These are patients with a severely dilated non-viable left ventricle, severe refractory pulmonary hypertension and right-sided heart failure, very low peak oxygen consumption (with or without signs of multi-organ failure) (Table 6.2). Such patients would more likely benefit from the implantation of an assist-device or heart transplantation, rather than from MVA.

In less advanced (stage C) heart failure, mitral valve repair should be considered. High-risk non-responders to medication and/or CRT with severe MR and a prohibitive surgical risk can benefit from percutaneous mitral valve repair using MitraClip. Non-responders with a lower peri-operative risk can benefit from surgical MVA, which provides more effective and stable mitral valve repair than percutaneous approaches. If available, a minimally invasive access, without a sternotomy, is preferable.

It is worth noting that some patients should be immediately considered for an early aggressive approach including CABG and/or MVA. These are the patients with significant angina pectoris or myocardial ischemia, left main or proximal LAD disease, extensive hibernating myocardium or severe mitral valve tethering.

Once heart surgery has been scheduled, the next critical question is the selection of individuals who will benefit from isolated CABG, and thus will avoid the increased peri-operative risk associated with concomitant MVA. Severe functional MR is not usually improved by revascularization alone and persistent MR, after isolated CABG, may hinder contractile LV function recovery and reverse LV remodeling. Therefore, in cases of
severe functional MR, the current expert consensus recommends concomitant restrictive MVA at the time of CABG. Table 6.3 shows the clinical and echocardiography pro and con characteristics for performing MVA in patients with ischemic and non-ischemic cardiomyopathy and functional MR. MVA should be considered in patients with severe MR undergoing concomitant CABG and with a low prevalence of comorbidities. Patients who will likely experience long-term benefit from MVA are those with a less dilated left ventricle, higher LV ejection fractions and significant myocardial viability (Figures 6.6). All patients with significant LV dyssynchrony undergoing CABG should receive CRT either before or soon after CABG. This recommendation is based on a recent study which showed that in the majority of patients, CABG alone is insufficient to eliminate pre-CABG dyssynchrony. Moreover, persistent post-CABG dyssynchrony hampers LV functional recovery and reduction of MR, which negatively impacts the prognosis.

Figure 6.6

Decision making regarding MVA in patients with severe functional MR in ischemic cardiomyopathy: the key characteristics associated with favorable clinical outcomes and durability of mitral valve repair
On the other hand, in patients with moderate functional MR undergoing CABG, the indication for concomitant mitral valve repair is highly controversial. Based on the findings of our and other studies, a practical approach for the management of patients with moderate MR undergoing CABG can be proposed (Figure 6.7) \(^{17, 18, 23-25, 45, 46, 48-55}\). In patients with a potential for LV functional recovery (i.e. significant myocardial viability, which includes the papillary muscles, without significant LV remodeling and LV dyssynchrony) and without a high-degree of mitral valve tethering, we have observed that favorable changes in MR after isolated CABG appear to be fairly predictable, with a majority (93%) of individuals showing MR improvement following revascularization alone. Reduction in MR is accompanied by alleviation of symptoms, reverse LV remodeling, and improved long-term outcomes. In all other combinations (i.e. absence of viable myocardium, presence of high-degree LV remodeling, LV dyssynchrony or significant mitral valve deformation), which represents roughly 2/3s of patients, changes in MR, after isolated CABG, are unpredictable, suggesting that concomitant MVA may be necessary \(^{24, 45}\).

**Figure 6.7**

Decision making regarding MVA in patients with moderate functional MR undergoing CABG.
Conclusions. Functional MR is caused by disease of the left ventricle with secondary distortion of mitral valve geometry. There is also strong evidence that the severity of LV disease and not the degree of MR is the major determinant of survival. Hence, causal therapy to manage MR should primarily address the underlying mechanism leading to the disease of the left ventricle and induce reverse LV remodeling. Optimal heart failure therapy, CRT, myocardial revascularization, percutaneous mitral valve repair using MitraClip or surgical MVA are all associated with reverse LV remodeling and reduction of MR. Timing and selection of interventions should be tailored to individual characteristics. All treatable components of heart failure, such as LV dyssynchrony, ischemia, hibernation or tachyarrhythmias, should be promptly identified and treated. In the majority of patients, onset of reverse LV remodeling will be accompanied by reduction of MR with diminishing LV volume overload, which in turn will lead to additional reverse LV remodeling with further long-term reduction of MR. Having said that, it is clear, that patients with the potential for reverse LV remodeling, i.e. those with the significant myocardial viability, will gain the greatest benefit from all of the above mentioned therapeutic modalities. The effects of each therapy should be continuously monitored and in the absence of a favorable response, other therapeutic options should be promptly considered and delivered before LV dysfunction progresses to an irreversible stage. On a similar note, authors of this chapter believe, that performing mitral valve repair early in the disease course, i.e. in patients with dynamic MR, can be more effective than waiting until development of late advanced disease, i.e. severe fixed MR. In conclusion, despite the lack of randomized studies, results of observational studies are promising and appear to suggest that, in selected patients, functional MR is a treatable complication of systolic heart failure provided that appropriate therapeutic interventions occur early in the disease course.
### Table 6.1 Assessment of therapeutic effects on systolic heart failure

<table>
<thead>
<tr>
<th>Therapy success</th>
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<tbody>
<tr>
<td>Mortality</td>
<td>Alive</td>
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<tr>
<td>HF hospitalization</td>
<td>-</td>
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<tr>
<td>NYHA functional class</td>
<td>I-II</td>
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<tr>
<td>NT proBNP, pg/ml</td>
<td>&lt; 1000</td>
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<tr>
<td>LV filling pressures</td>
<td>Normal or slightly ↑</td>
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<tr>
<td>Reverse LV remodeling</td>
<td>+</td>
</tr>
<tr>
<td>Functional MR ERO, mm² (grade) Rest: ERO &lt; 20 (≤2/4) Exercise: ERO increase &lt; 13 (≤2+/4)</td>
<td>Rest: ERO ≥ 20 (&gt;2/4) Exercise: ERO increase ≥ 13 (&gt;2+/4)</td>
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Abbreviations: ERO = effective regurgitant orifice; ↑ = elevated

### Table 6.2 When is it too late to perform mitral valve repair

<table>
<thead>
<tr>
<th>Myocardium-related factors</th>
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<tr>
<td>HF duration ≥ 5 y or LVEDd &gt; 65-70 mm for ischemic CMP</td>
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<tr>
<td>≥ 8 y for or LVEDd &gt; 75-80 mm for non-ischemic CMP</td>
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<tr>
<td>Non-viable myocardium</td>
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<td>Fixed pulmonary hypertension and/or refractory RV failure</td>
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<th>Peak VO₂ max &lt; 14 mg/kg/min</th>
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<table>
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<tr>
<th>Systolic blood pressure &lt; 80 mmHg</th>
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<tr>
<th>Multiorgan failure</th>
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<tbody>
<tr>
<td>Serum sodium &lt; 135 mmol/l</td>
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<tr>
<td>Creatinine &gt; 2.5 mg/dl</td>
</tr>
<tr>
<td>Elevated serum bilirubin</td>
</tr>
<tr>
<td>Cachexia</td>
</tr>
</tbody>
</table>

Abbreviations: CMP = cardiomyopathy, LVEDd = left ventricular end-diastolic diameter, RV = right ventricular
Table 6.3 Key clinical and echocardiography points for decision making regarding surgical mitral valve repair in patients with systolic heart failure of ischemic and non-ischemic origin.

<table>
<thead>
<tr>
<th></th>
<th>Ischemic cardiomyopathy</th>
<th>Non-ischemic cardiomyopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>MV repair +</td>
<td>MV repair -</td>
<td>MV repair +</td>
</tr>
<tr>
<td>MV repair -</td>
<td>MV repair -</td>
<td>MV repair -</td>
</tr>
<tr>
<td>Functional MR</td>
<td>Severe (rest or exercise)</td>
<td>Stable moderate</td>
</tr>
<tr>
<td></td>
<td>Severe (rest or exercise)</td>
<td>Stable moderate</td>
</tr>
<tr>
<td>Perioperative mortality risk, %</td>
<td>&lt; 5</td>
<td>≥ 5</td>
</tr>
<tr>
<td></td>
<td>&lt; 5</td>
<td>≥ 5</td>
</tr>
<tr>
<td>CABG</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>LVEDd, mm</td>
<td>≤ 60 (♀), ≤ 65 (♂)</td>
<td>&gt; 60 (♀), &gt; 65 (♂)</td>
</tr>
<tr>
<td></td>
<td>≤ 60 (♀), ≤ 65 (♂)</td>
<td>&gt; 60 (♀), &gt; 65 (♂)</td>
</tr>
<tr>
<td>LVEDd (mm) and</td>
<td>EDd 61-65 (♀), 66-70 (♂)</td>
<td>EDd 61-65 (♀), 66-70 (♂)</td>
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<td>Myocardial viability</td>
<td>+ viable myocardium</td>
<td>+ non-viable myocardium</td>
</tr>
<tr>
<td></td>
<td>+ viable myocardium</td>
<td>+ non-viable myocardium</td>
</tr>
<tr>
<td>Myocardial viability</td>
<td>≥ 5 segments</td>
<td>≥ 5 segments</td>
</tr>
<tr>
<td></td>
<td>EF ≥ 10% at DSE</td>
<td>EF ≥ 10% at DSE</td>
</tr>
<tr>
<td></td>
<td>&lt; 5 segments</td>
<td>≥ 5 segments</td>
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<tr>
<td>LV ejection fraction, %</td>
<td>≥ 30</td>
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</tr>
<tr>
<td></td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Duration of HF, y</td>
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<tr>
<td></td>
<td>&lt; 8</td>
<td>≥ 8</td>
</tr>
</tbody>
</table>

Abbreviations: DSE = dobutamine stress echocardiography, HF = heart failure, LVEDd = left ventricular end-diastolic diameter
References


77. Pu M, Thomas JD, Gillinov MA, Griffin BP, Brunken RC. Importance of ischemic and viable myocardium for patients with chronic ischemic mitral regurgitation and left ventricular dysfunction. Am J Cardiol. 2003;92(7):862-864.


7. **Novel Catheter-Based Approaches in Treatment of Heart Failure**

Advances propelled by the translational medicine or technology development lead to novel biologic or device based therapeutic interventions aiming to fill this therapeutic gap and halt or reverse the vicious cycle of heart failure progression. A substantial advances have been made in identifying the molecular mechanisms propelling the heart failure progression (Figure 7.1 and 7.2).

**Figure 7.1**

Factors and mechanisms involved in the heart failure progression being potential therapeutic targets in the heart failure treatment. HFrEF: heart failure with reduced ejection fraction; HfPEF: heart failure with preserved ejection fraction; HR: heart rate; FMR: functional mitral regurgitation; MLMP: matrix metalloproteinases; LV: left ventricle.

It is critical to keep in mind the multifactoriality of the heart failure etiology and progression when considering the device based approach. One needs to keep in mind the options as they should be tailored to the disease presentation and individual patient profile. In this review, we summarize recent developments with regard to treatment of chronic heart failure as they are designed to target various components in the cascade heart failure progression...
aimed to fill the gap in the therapeutic strategies of advanced heart failure (Table 7.1). For the didactic purpose, potential targets for device-based interventions can be divided into 3 groups: mechanical, electrical and neuromodulatory targets.

**Figure 7.2**

The cascade of chronic heart failure progression and the potential therapeutical approaches. Novel approaches are targeting to fill gaps in therapeutic strategies of advanced heart failure.

**Left ventricular restoration.** Progressive left ventricular dilation is one of the hallmarks of heart failure progression. Though serving initially as a compensatory mechanism to sustain the stroke volume and ventricular function, it is also associated with increased wall stress, thereby further precipitating progressive ventricular enlargement and failure. Specific subsets are patients with large transmural myocardial anterior infarction where transmural damage with development of a- or dyskinetic infarcted segments due to the wall thinning may precipitate infarct expansion with elongation of the affected region. In accordance with Laplace law, the altered ventricular geometry underlies increased regional wall stress and regional overload which further aggravates abnormal local mechanics, adversely affects remote myocardial segments and perpetuates further ventricular dilation. Though initially these mechanisms may contribute to the maintenance of ventricular pump function, this
self-perpetuating cycle ultimately results in spherical chamber remodeling and reduced forward stroke volume. Reduction of the wall stress by reducing the ventricular cavity has been attempted previously surgically with aneurysma resection or using mesh like devices to support cardiac mechanics and limit further dilation. However, none of these approaches has reached wide clinical adoption so far.

Reduction of the wall stress by shrinking the ventricular cavity has been traditionally attempted surgically. Recently, Parachute™ device (CardioKinetix Inc., Menlo Park, CA, USA) has been introduced to restore ventricular geometry and cardiac mechanics (1). The intervention aims to partition distal dysfunctional segments that are non-contributory to the ventricular mechanics and forward cardiac output. The partitioning is achieved using a parachute-shaped device excluding dysfunctional apical segments from mid and basal segments with preserved contractile function (Figure 7.3). In other words, the Parachute™ device partitions the enlarged ventricle into a “dynamic” and a “static” chamber, where the latter becomes practically excluded from the circulation, normalizing the physiologic conical shape of the dynamic chamber, as well (1, 2).

The device consists of an umbrella-like flexible nitinol frame, covered with poly-tetra-fluoro-ethylene surface. The nitinol frame provides a stable and well-expanded position below the papillary muscles, leaning against the apex. The flexible frame allows the device to follow the contractions of the ventricle, thereby imitating the native movements of the apex. Conceptually, the system facilitates ventricular torsion mechanics and physiologic blood flow dynamics: the stress is transposed from the weakened myocardial segments to the nitinol frame, generating supportive work in diastolic filling due to its flexible physical characteristics. In this regard, the device can hypothetically contribute to the twisting-untwisting mechanics and to the reduction of the intraventricular wall stress, improving overall myocardial efficiency. Animal data support this concept, demonstrating a leftward shift in the pressure-volume relationships (1).

Clinical experience is has been gathered in various registries and single center experience (2, 3) or initial PARACHUTE trial (4). Clinical experience so far indicates overall favorable safety profile with several signals of the improvement as regards the clinical symptoms, cardiac structure and function and physical fitness. Our personal perspective and experience with this innovative approach to modify left ventricular geometry points also at favorable safety profile. The key is the appropriate patient selection in the subgroup of
symptomatic patients with chronic heart failure after extensive anterior myocardial infarction and relevant apical scar. The pre-procedural selection and planning is driven by computed tomography or magnetic resonance imaging, determining the anatomic suitability for the intervention. The procedure requires smooth peripheral vascular access. Care should be paid to the aortic valve crossing, which has been recently facilitated by improvements in guide design and sizing. The implantation itself should aim at restoration of the near-physiologic geometry. Therefore, taking into account the pre-procedural evaluation an accurate 3-dimensional thinking is required for proper positioning of the device. Various sizes are available expanding the patients’ eligibility and anatomic substrate. Postprocedural systemic anticoagulation is required at least for one year, however the need for longer anticoagulation treatment is unclear. Further randomized studies are ongoing to establish its clinical value in treatment of post-infarct heart failure (5).

**Figure 7.3**

![Remodeled left ventricle after extensive anterior myocardial infarction can be functionally divided into a dynamic- and a static space (indicated in Panel A – lower picture). Parachute™ device (CardioKinetix Inc., Menlo Park, CA, USA) aims to partition distal dysfunctional segments that are non-contributory to the ventricular mechanics and forward cardiac output and exclude them from blood circulation in order to restore the near-physiologic shape and structure of the left ventricle. (indicated in Panel B)](image)

Alternative device targeting ventricular remodeling is the Revivent™ myocardial anchoring system (BioVentrix Ltd, San Ramon, CA, USA) by applying the left ventricle plication. Left ventricular plication is performed through a minimal invasive transthoracic
approach by placing anchoring stitches through the infarcted area, between the right-ventricle side of the septum and the epicardial surface of the left ventricle. Fastening the stitches the infarcted muscle can be plicated, and so the volume of the left ventricle can be reduced. First-in-man study included 26 patients with severely reduced left ventricle systolic function (EF 13-43%) after anterior myocardial infarction. At the 6-month follow-up, a marked reduction of the left ventricle dimensions (reduction in end-diastolic volume index and end-systolic volume index 29.9% and 35.0%, respectively), and moderate improvement in functional status (NYHA class 2.5 versus 1.7) were observed (abstract presentation TCT 2012).

LV diastolic restoration. Diastolic heart failure or heart failure with preserved left ventricular ejection fraction (HFPEF) is characterized by abnormal relaxation and chamber stiffness. There is no causative therapy for diastolic heart failure. The main therapeutic goal should be to enhance diastolic relaxation by prolonged diastolic time, to reduce myocardial stiffness in tandem with afterload and volume reduction. The conventional medical therapy includes vasodilators, agents blocking the renin-angiotensin system and mainly diuretics including aldosterone blockers, which remain the mainstay in the management of HFPEF.

Elevated left atrial pressures and pulmonary congestion related to backward failure belong to hallmarks of severe HFPEF or systolic dysfunction. Recently, new catheter-based approaches were proposed to reduce left atrial pressure and ventricular decompression: IASD™ (Corvia Medical Inc., Tewksbury, MA, USA) (Figure 7.4 - left) and V-Wave Shunt™ (V-Wave Ltd, Or Akiva, Israel) (Figure 7.4 - right). Both are designed to create a controlled atrial septal defect in symptomatic patients with heart failure. While W-Wave Shunt™ device is tested in both systolic and diastolic heart failure (6), IASD™ device is being evaluated in patients with symptomatic heart failure and ejection fraction ≥40% (8, 10). The feasibility and early safety profile of both device-based approaches has been demonstrated in the initial studies (6, 7) The authors have personal experience with use of the IASD device (within the context of the REDUCE Elevated Left Atrial Pressure registry with primary goal to evaluate safety and performance of the device implant) (8). The device is percutaneous implantable through conventional venous access and transseptal puncture. The selection in the registry has been guided by the clinical and hemodynamic criteria including levels of LV filling pressures at rest or during the supine exercise. The procedure itself is straightforward. After trans-septal puncture, the preloaded device is advanced to the left atrial site of the
septum. Then, the left atrial side of the device is released under echocardiographic and fluoroscopic guidance followed by slight retraction of the handle and release of the right atrial side. Postprocedural regimen includes Aspirin 75-325 mg ad vitam. Concomitant use of other antiplatelet or anticoagulant regimen is prescribed per institutional practice or individual patient profile. First outcome data are to be presented at upcoming ACC 2016 meeting.

Figure 7.4

Upper panels: IASD™ (Corvia Medical Inc., Tewksbury, MA, USA) (left) and V-Wave Shunt™ (V-Wave Ltd, Or Akiva, Israel) (right). Both are designed to create a controlled atrial septal defect in symptomatic patients with heart failure. Lower panels: 3D echocardiographic appearance of the IASD device after the deployment in the left atrium (left) and final fluroscopic appearance of the device after the complete deployment implantation (right).
**Electro-myocardial targets.** Devices aiming at *electro-myocardial targets* include mainly cardiac resynchronization therapy and implantable cardioverter defibrillators which represent the mainstay in the modern heart failure management. In addition, novel electrical modalities beyond pacing have been conceived for treatment of heart failure.

The concept of Cardiac Contractility Modulation (CCM) has been under study for more than a decade. CCM is based on a delivery of low-energy stimulations during absolute refractory period of action potential or so called non-excitatory electrical impulses on the myocardium. Preclinical experience including histological and molecular-biological analyses suggest that well-timed non-excitatory impulses can improve cardiac contractility through phosphorylation and gene expression of calcium handling proteins. In particular, in isolated myocytes obtained from canine model of chronic heart failure, non-excitatory stimulation resulted in improved contractile function in parallel with increased intracellular peak Ca$^{2+}$ levels. Likewise, in vivo assessment demonstrated improvements in indices of cardiac function and contractility. The clinical translation has been facilitated by a pacemaker-like device called Optimizer$^\text{TM}$ III (*Impulse Dynamics Germany GmbH., Willich, Germany*). In the largest, randomized trial performed to investigate the clinical value of CCM in patients with CHF 164 patients were enrolled (9). The study reported significant improvement in oxygen consumption and Minnesota Quality of Life suggesting clinical benefit related to CCM therapy in CHF.

**Neuro-modulatory targets.** Increased sympathetic tonus and neurohumoral dysbalance is one of the main pathophysiological mechanisms contributing to heart failure progression. Large clinical trials provided proof-of-concept that pharmacological sympathetic blockade with betablockers improves morbidity and mortality of heart failure patients. This evidence is the stepping stone for device based interventions targeting the neurohumoral axis such as renal denervation therapies and vagal stimulation (10).

**Renal Sympathetic Nervous System.** The key-role of the renal sympathetic nervous system (RSNS) in the general sympathetic activation of blood pressure, volume control and overall homeostasis is well known. Changes in renal blood flow due to pressure drop lead to its activation and increased activity of the Renin-Angiotensin-Aldosterone System (RAAS) resulting in compensatory efferent renal vasoconstriction, natrium retention and rise of blood pressure. Given that RAAS is actively connected to general sympathetic nervous system, its activation stimulates the central sympathetic pathways through efferent nerves,
resulting in catecholamine rise, systematic vasoconstriction, and signs of sympathetic hyper-reactivity. On the other hand, RAAS can be activated also through afferent renal nerves from the central sympathetic network closing the centro-renal sympathetic loop. In this loop, a minor stimulative effect can lead to marked sympathetic reaction, critical for development of hypertension or perpetuating the vicious circle heart failure progression.

The relevance of the sympathetic nervous system in heart failure progression is well established. Increased sympathetic activity is associated with worse outcome. In particular, elevated serum catecholamine levels, higher heart rate, lower heart rate variability are hallmarks of poor prognosis and linked to higher mortality. Non-pharmacological blockade by targeting the para-renal sympathetic plexus offers a possibility of a more complete and permanent disruption of hyper-reactive centro-renal sympathetic loop. The concept of eradicating the para-renal sympathetic nerves has been initially attempted surgically, however, due to its invasive nature it did not gain wider application. Recently, percutaneous Renal Denervation Therapy has been introduced to ablate the renal sympathetic plexus with the RF energy. Rapid development led to introduction of several devices including the Ardian™ (Medtronic Inc, Minneapolis, MN, USA), the Vessix™ (Boston Scientific Corp, Natick, MA, USA) or EnligHTN™ (St. Jude Medical, St. Paul, Minnesota, USA) systems. All these devices were primarily investigated in the context of uncontrolled arterial hypertension. Given the pathophysiological basis, it is attractive to hypothesize that similar interventional approach may be effective also in the setting of heart failure with primarily higher sympathetic activity such as diastolic heart failure or subsets of chronic heart failure with reduced ejection fraction. The REACH pilot-study (REnal Artery denervation in Chronic Heart failure) tested the feasibility of renal denervation in 7 heart failure patients (11). The procedure was well tolerated and at 6 months, all patients showed lower NYHA class and improved 6-minutes walking test. This feasibility study opens the possibility for larger randomized trials with rigorous design to address potential benefits of renal denervation therapy in patients with CHF.

Carotid baroreceptors modulation. The carotid baroreceptors play a key role in the sympathetic-parasympathetic regulation and their stimulation can markedly increase the parasympathetic tone and inversely reduce the general sympathetic activity. Parasympathetic stimulation and vagal reflexes can positively modulate mortality outcomes in experimental models of myocardial ischemia or heart failure (12, 13). These pathophysiological findings
provided the basis for development of devices designed for continuous electrical stimulation of carotid baroreceptors to reduce sympathetic activity and modulate heart failure presentation. BaroStim™ is a novel programmable pacemaker-like device, which provides the opportunity for a personalized stimulation rate of the baroreceptors. The device has been widely tested in patients with therapy resistant hypertension (14). Whereas, a limited experience was obtained in diastolic heart failure (15), no experience has been reported yet in systolic heart failure.

Vagal nervous system. The vagal nerve is the backbone of parasympathetic regulation and may serve as a potential target for stimulation to restore the neuro-humoral imbalance towards the parasympathetic dominance. The neuro-stimulator (CardioFit 5000, BioControl Medical, Yehud, Israel) is designed for low-energy stimulation of the vagal nerve. It consists of a pacemaker-like low-energy generator, a stimulating electrode to deliver paces and a sensor electrode for appropriate timing. The generator is implanted in the right subclavian fossa, similar to conventional pacemakers. The stimulating electrode, is positioned distally to the right vagal nerve few centimeters below the carotid bifurcation. The sensing electrode is placed in the right ventricle of the heart. The device is programmable to adjust parameters for the most optimal stimulation. The timing of stimulation is set to a fixed delay (70 ms) from the R wave. First-in-man experience has been reported by De Ferrari et al. in 32 patients with NYHA II-III heart failure. Implant has been associated with two procedure-related serious adverse events (16) During 6 month follow-up two deaths occurred due to progression of the heart failure. At 6 month follow-up, significant improvement in 6-minutes walking test, in Minnesota Quality of Life Index, in Left Ventricle Systolic Volume Index and in Ejection Fraction was observed in the remaining patients, an effect that persisted up to 12 month follow-up completed in subset of patients. On the other hand, NECTAR-HF study with the sham controlled procedure, reported improved quality of life while failing to detect improvements in indices of functional capacity and remodeling (17). The INOVATE-HF study (INcrease Of VAgal TonE in CHF) (18) is a phase III study that should determine beneficial effects of the device on the hard clinical end-points in a large population.

Alternative approach to vagal stimulation has been introduced by devising a device stimulating aortic arch afferent vagal nerves. Aorta contains sensory regions that sense the changes in pressure and arterial wall stress affecting the cardioregulatory centrum that via efferent signaling increases the parasympathetic tone. Based on these findings, Enopace
(Israel) has developed a stent-like device (Harmony) that after implantation in the distal part of the aortic arch to activate the aortic afferent fibers leading of the left vagal trunk. Conceptually, the afferent signals should modulate neural pathways and reduce arterial stiffness and thereby favorably modifying the afterload in combination with a reduction of the peak systolic pressure. The proof-of-concept study is now being initiated in Europe.

**Future perspectives.** Considering the mechanisms of heart failure, namely impaired myocardial function on cellular, on tissue and on system level, it is no question that medical therapy targeting symptoms and deleterious compensatory mechanisms remains the mainstay in state-of-the-art management of heart failure. Cardiac resynchronization therapy is the first example of successful device based interventions altering the adverse course of heart failure. Its success as well as detailed knowledge of factors and mechanisms contributing to heart failure progression facilitated the development of device-based interventions for treatment of chronic heart failure. While the assist devices are aiming at the end-stage heart failure, emerging device-based percutaneous or minimal invasive techniques comprise the wide spectrum of innovative concepts that target ventricular remodeling, cardiac contractility or neuro-humoral modulation. The clinical adoption is in the early stages of the initial feasibility and safety studies and clinical evidences need to be gathered in the appropriately designed clinical trials.
<table>
<thead>
<tr>
<th>Target</th>
<th>Device</th>
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<tbody>
<tr>
<td><strong>Mechanical</strong></td>
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</tr>
<tr>
<td>Systolic restoration</td>
<td>Parachute™ percutaneous left ventricle partitioning device for patients with apical wall motion abnormalities</td>
</tr>
<tr>
<td></td>
<td>Revivent™ percutaneous left ventricle plication device for patients with antero-apical scar</td>
</tr>
<tr>
<td>Diastolic function</td>
<td>ImCardia™ epicardially placed metallic coils using the bow-string effect to restore diastolic function</td>
</tr>
<tr>
<td></td>
<td>CORolla™ endocardially placed metallic coils using the bow-string effect to restore diastolic function</td>
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<td></td>
<td>IASD™ interatrial shunt device for reduction of therapy resistant increased left atrial pressure</td>
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<tr>
<td>V-Wave</td>
<td>interatrial shunt device for reduction of therapy resistant increased left atrial pressure</td>
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<td>Optimizer™ cardiac contractility modulation with non-excitatory stimuli of the myocardium</td>
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<tr>
<td><strong>Neuro-modulatory</strong></td>
<td>RDN renal denervation therapy for reducing baseline sympathetic activity in systolic CHF</td>
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<td>BaroStim™ continuous stimulation of the carotid barorceptors for reducing sympathetic activity in heart failure</td>
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<td>CardioFit™ chronic vagal nerve stimulation modulation of autonomic imbalance</td>
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References


8. CARDIAC REGENERATIVE INTERVENTIONS IN HEART FAILURE: CLINICAL TRANSLATIONAL EVALUATION

Jozef Bartunek and Andre Terzic

Stem cell-based regenerative medicine offers an expanded therapeutic armamentarium that drives the evolution of medical sciences from traditional symptom mitigation to previously unreachable curative algorithms. Stem cells demonstrate a unique aptitude to differentiate into specialized cell types, and to form new tissue providing thereby the active ingredient of regenerative regimens (1). Regenerative approaches target functional restoration of damaged heart tissues not mere alleviation of disease symptomatology. In general, successful application of regenerative medicine principles bears the promise of significant human health benefit with tangible outcomes for an improved patient care and an increased quality of life (2)

The present overview highlights the rationale for regenerative approaches; targets and mechanisms of therapy delineated respectively for acute versus chronic disease, implicating both direct and indirect modes of action; cell delivery techniques which have catalyzed early translation of stem cell-based treatment; stem cell platforms which define the spectrum of available biotherapeutics; and ultimately the clinical experience to date, providing a synopsis of cardiovascular regenerative medicine from principles to practice.

Innate cardiac rejuvenation. Traditionally, the human heart has been viewed as a terminally differentiated postmitotic organ in which the number of cardiomyocytes is established at birth, and these cells persist throughout the lifespan of the organ and the organism. However, the discovery that cardiac stem cells live in the heart and differentiate into the various cardiac cell lineages has changed profoundly our understanding of myocardial biology (3, 4). Cardiac stem cells regulate myocyte turnover and condition myocardial recovery after injury. This novel information imposed a reconsideration of the mechanisms involved in myocardial aging and presence of the innate molecular mechanisms capable of regeneration. Indeed, the unexpected recognition that the heart is not a terminally-differentiated organ, but rather harbors self-repair mechanisms to maintain tissue homeostasis has been recently documented and validated (Figure 8.1).
In fact, radio-isotope decay-based study demonstrated that more than half of the heart mass can be renewed over a lifespan (5). Cardiomyocyte turnover rate has been estimated at least at about 1% per year in young adults, and decreases to 0.5% per year in elderly individuals. Stem cell contribution to postnatal heart formation has been also validated by the self/non-self chimerism characteristic of patients following allogeneic transplantation (6). Furthermore, evidence has been gained that stem cells can migrate from circulation or other residing organs such as bone marrow to the heart in response to the injury (6). Despite disrupting the conventional historical postulates, the native regenerative potential is
insufficient to rescue myocardium in response to massive injury. The overall efficiency of self-repair is further compromised by age, disease status, co-morbidities or concomitant drug therapies. Nevertheless, the paradigms of the potential natural heart rejuvenation in tandem with the concepts of transplant-based organ replacement point at the activation of endogenous repair and/or introduction of exogenous progenitor cells into the injured infarcted heart as compelling strategies for therapeutic cardiac repair (7).

**Targets and mechanisms of regenerative therapy.** Stem cell therapy is designated to halt or reverse the progression of myocardial injury. Time-dependent multidimensional interactions between cardiomyocytes, extracellular matrix, the immune-inflammatory response and perfusion together determine the outcome of global remodeling and ventricular performance throughout the healing response. Early after myocardial injury, the primary therapeutic goal is the salvage of the jeopardized myocardium to prevent myocardial expansion and pathologic remodeling. At later stages of developed left ventricular dysfunction, the aim is to reverse maladaptive remodeling and ensure improved cardiac performance (8). In particular, excessive inflammatory response, oxidative stress and apoptosis are the primary targets in initial stages, whereas fibrosis, loss of fibre organization, and impaired excitation-contraction coupling are key features of advanced heart failure. Thus, differences in the molecular and cellular substrates during the course of disease may require distinct regenerative strategies to prevent progression or treat overt heart failure (8).

The mechanisms ascribed to improvements after cell delivery are still subject of the intensive research but seem to be chiefly mediated by paracrine mechanisms rather then substantial de novo myocyte replacement. (8-11). In this principle mode of action, delivered stem cells interact with the injured/diseased myocardium and its microenvironment and induce reparative signaling to modulate inflammation, ischemic tolerance, endogenous healing. Several indirect mechanisms have been proposed, including activation of endogenous cardiac progenitor cells, stimulation of cardiomyocyte division, and modification of the tissue niche with increase in neovascularization and reduction in scar burden (10). Taken together, current repair models have been revisited to include augmentation of endogenous capacity for neoangiogenesis, myocardial cytoprotection, and activation of reparative resident cardiac stem cells as main contributing mechanisms of the overall stem cell benefit.
**Modes of cell delivery.** Safe and efficient delivery of a sufficient amount of a stem cell-based biotherapeutics is essential to trigger processes of repair while ensuring minimal off-target delivery and diffuse cell dissemination (12). Distinct delivery routes have been tested (Figure 8.2).

**Figure 8.2**

They include systemic, i.e., intravenous injection, versus myocardially-targeted approaches, such as percutaneous intracoronary delivery, endomyocardial injection, and in the context of cardiothoracic surgery epicardial injections (12). Peripheral intravenous delivery is the least invasive, but provides the lowest degree of myocardial homing and would be applicable if the mode of action solely relied upon paracrine/endocrine secretion into the circulation. Though limited, if optimized this approach would be an attractive option due to the broad accessibility in clinical practice. Recent pre-clinical studies have provided proof-of-concept by demonstrating benefit without the need for homing due to the bioavailability of secreted anti-inflammatory proteins from the peripheral circulation. Alternatively, intracoronary delivery has been utilized to date by most of the clinical trials.
testing the cell therapy early after myocardial infarction. Endo-myocardial delivery through endocardial transplantation has been typically applied utilized in chronic heart failure as a stand alone procedure. Although historically first introduced in the context of cell delivery, epicardial cell transplantation is limited to patients with a primary indication for heart surgery.

Using currently available techniques, delivery of stem cells demonstrates variable retention rates, typically not exceeding 5-10% of the injected dose regardless of the method of administration. Progressive decrease in myocardial signals after delivery of labeled stem cells is consistent with rapid cell death or washout, within hours of administration. Although this limitation does not invalidate the efficacy of stem cells, it does suggest that reparative mechanisms involve paracrine or immunomodulatory processes that may not require local preservation of the regenerative biologics. On the other hand, low retention rates undermine the pharmacological efficacy of the regenerative strategies. In fact, the biodistribution of stem cells is variable, depending in part on the cell type, with cells potentially reaching remote organs such as the lungs, liver, or spleen. Although safety issues have not been raised, the consequence of extra-cardiac homing is unknown. Accordingly, long-term biovigilance has been incorporated in the development algorithm of stem cell products. In addition, a concerted effort in clinical development is required to optimize the efficient and safe delivery to dysfunctional but viable myocardium. Long-term engraftment is dependent on a number of possible influences including method of delivery, proper supply of nutrients or, cotransfer of supporting cell types such as fibroblasts or endothelial cells, hydrogels or matrix components and immune rejection. Various strategies are being tested focusing on various interactions between cells, device and myocardial tissue (Figure 8.3). In this regard, we have recently developed a novel catheter for the endomyocardial delivery with modified curved needle design and side holes, yielding improved retention rates as compared to conventional straight needle design. Finally, additional advances and implementation of the novel imaging techniques including the image fusion and 3D reconstruction should further facilitate the accuracy and efficacy of the targeted cell delivery.
Stem cell platforms and clinical trial experience. Cell-based therapy includes autologous and allogeneic interventions. Autologous stem cells are derived from non-cardiac or cardiac self-sources, thereby avoiding immune intolerance. The main source are bone marrow, cardiac tissue or adipose-tissue derived stem cells. Applications for autologous stem cells are typically limited to chronic conditions given the time required to recycle stem cells from patients serving as donors through the stages of mobilization, collection, expansion, and preparation for delivery back to the same patient now serving as the recipient. In contrast, allogeneic stem cells are derived from a selected donor who is different from the recipient. In principle, allogeneic approaches can produce immune mismatch, including a host-versus-graft reaction where engrafted stem cells are recognized as non-self and attacked by the host. Yet, allogeneic tissue offers unique advantages, including the ability to generate master cell banks and store therapeutic doses to be available “off-the-shelf” for acute/subacute use or in cases where a patient has a genetically based disease that would in principle hinder the therapeutic potential of the autologous stem cell pool.

Cell-based products are regulated advanced medicinal products and must be carefully designed and validated to ensure consistency and traceability. Control and management of manufacturing and quality-control testing are carried out according to Good
Manufacturing Practice requirements. Screening for purity, potency, infectious contamination, and karyotype stability have become necessary elements, i.e., release criteria, in compliance with standard operating practices for production and banking of cells used as autologous or allogeneic therapy. Accordingly, regulatory agencies impose guidelines for risk assessment, quality of manufacturing, preclinical and clinical development, and post-marketing surveillance (13, 14).

Regenerative stem-cell based platforms include natural versus engineered stem cells. Examples of naturally derived stem cells range across the embryonic to adult stem cell spectrum (15). The newest technology of nuclear reprogramming enables moreover derivation of induced pluripotent stem cells, an example of an engineered stem cell platform (16). Distinct stem cell types display advantages and challenges associated with availability of the source tissue from which they are derived, differentiation capacity and pluripotent potential, tumorigenic tendency and immunogenic profile, and ultimately socioethical considerations (17).

Embryonic stem cells, derived from the inner mass of a developing embryo in the blastocyst stage, are considered the stem cell archetype. They harbor the capacity of self-renewal, can be clonally expanded and are capable of differentiating into any cell type in the body, including functional cardiomyocytes (18). Despite robust cardiomyogenic potential, significant obstacles limit their clinical translation, including risk for uncontrolled growth and immune rejection, in addition to fundamental ethical issues. In this regard, remarkable advances have been made in generating embryonic-like stem cells through dedifferentiation of somatic cells, providing an alternative and embryo-independent pluripotent source for derivation of cardiogenic lineages (19) While applications for diagnostic and toxicology applications are already advanced, induced pluripotent stem (iPS) cell-based therapeutic use faces a number of challenges, including risk of teratoma formation associated with pluripotency, time required to derive and characterize iPS cells obtained from any given patient, possible genetic instability, and ultimately low efficiency of cardiogenic differentiation (20).

Adult skeletal myoblasts, bone marrow or peripheral blood stem cells were in fact among first to be investigated in a clinical setting for cardiac regeneration. Skeletal myoblasts, expanded from a thigh muscle biopsy, are conceptually attractive due to a potential contractile phenotype, opportunity for autologous transplantation, and
resistance to ischemia (21). Skeletal myoblasts however differentiate into multinucleated myotubes, not apparently cardiomyocytes, after injection into the heart. Myotubes lack gap junctions, resulting in possible electrical inhomogeneity that could predispose to ventricular arrhythmia. The first prospective, randomized, placebo-controlled skeletal myoblast trial (MAGIC trial) used an epicardial approach for delivery, but exhibited overall lack of functional efficacy (22). Percutaneous intramyocardial delivery of skeletal myoblasts was alternatively applied in a subsequent trial (SEISMIC trial) which demonstrated symptomatic relief with however no significant effect on global left ventricular ejection fraction (23).

Clinical application of bone marrow and blood derived stem cells has been catalyzed by their easy accessibility and processing from a renewable source. Case in point, the adult bone marrow contains different cell populations, including monocytes, hematopoietic and mesenchymal stem cells. Human hematopoietic stem cells can be defined as CD34+ cells capable of reconstituting blood lineages and, possibly, the ability to trans-differentiate into cardiomyocytes, endothelial cells and smooth muscle cells in vivo. Mesenchymal stem cells can be defined as CD105+ CD90+ cells, isolated by preferential adherence to plastic in tissue culture, which are capable of osteogenic, chondrogenic and adipogenic differentiation, and under guidance to cardiogenic specification. In the clinical setting, autologous bone marrow derived mononuclear cells, unfractionated or enriched in progenitor subpopulations, have been most frequently used for treatment of acute myocardial infarction typically delivered via the intracoronary mode. Experience to date highlights an excellent feasibility and safety profile, generally positive clinical outcomes, although primary endpoints have not always been met and a sustained functional benefit remains uncertain. Indeed, meta-analyses of case-controlled trials in patients with recent myocardial infarction suggest controversial benefits at the level of various clinical and surrogate end-point readouts (24-26). Controversial readouts may relate to different study design, heterogenous patient populations, cell number and processing, time of cell injection, or methods used to assess outcome (27, 28). Larger trials are thus needed to dissect the true clinical potential of stem cell therapy early after myocardial infarction. The ongoing large EU-funded Bone Marrow Cells in Acute Myocardial Infarction (BAMI) trial will evaluate mortality benefits of bone-marrow stem-cell therapy in over 3000 reperfused myocardial infarction patients. The BAMI investigators will deploy the standardized techniques for cell processing and delivery. Because the short-term mortality following successful revascularization of a culprit artery is
already very low, studies looking for the benefit of stem-cell therapy may have to combine mortality, reinfarction, and heart failure into a composite end point. Also, health-related quality of life should be measured to judge the full benefit. In the setting of chronic heart failure, large phase III clinical study using allogeneic mesenchymal cells (so called mesoangioblasts) is also underway to determine the clinical benefits in patients with chronic heart failure.

As pointed out, overall trial results are not uniform owing to the current lack of standardization and optimization of cell isolation and delivery protocols. This lack of uniformity is prevalent despite newer techniques that allow point-of-care cell preparations, for example within cardiac catheterization or operating rooms, thereby providing short preparation time, facilitated logistics of cell transport, and reasonable cost effectiveness. Beyond inter-trial variability, inter-patient variability has been increasingly recognized triggering an ongoing quest for optimization and identification of the most appropriate cell source and cell type, stratification and selection of patient populations most amenable to cell-based therapy, targeting ideal timing of intervention and most favorable routes of administration. In this regard, it should be noted that in contrast to traditional small molecule-based medications, regenerative cell products contain life cells as the active ingredient. Moreover, cell therapy is currently limited by low rates of cell engraftment and poor cell survival. Advanced patient age, cardiovascular risk factors, and underlying heart disease appear to also have a negative impact on the functionality of delivered cells. The imperative to improve the benefits and reproducibility of cell-based products stimulated the development of the next generation stem cell products. Conceptually, they include products aiming for the anatomical matching using the heart as the regenerative cell source or expand this concept by aiming at growth factor promoted cardiovascular lineage commitment as a lead to reduce the variability in the stem cell function (29-31).

The first approach in the next generation stem cell products is based on the processing of myocardial tissue excised during cardiac surgery or by endovascular biopsy to derive resident stem cell populations (32) or cardiospheres (33). Clinical evaluation of resident cardiac stem cells has been initially tested in the SCIPIO (Cardiac Stem Cell Infusion in Patients With Ischemic Cardiomyopathy) and the CADECEUS (CArdiosphere-Derived aUtologous stem CElls to reverse ventricUlar dysfunction) trials. The CADECEUS study utilizes the cell cluster or cardiosphere approach for derivation and propagation (33) while SCIPIO
implements an antibody-based method to derive a homogenous C-kit+ population (32). CADECEUS focuses on individuals with subacute myocardial infarction, with harvest of the patient’s own biopsy-obtained right ventricular tissue to yield an autologous therapeutics delivered via coronary arteries. The SCIPIO study utilizes right atrial tissue obtained during coronary artery bypass for autologous, intracoronary (proximal coronary artery or graft supplying the infarcted left ventricular region) delivery of derived C-kit-expressing human cardiac stem cells. Both studies are first-in-man trials powered to assess safety and feasibility. Nevertheless, they both reported encouraging observatory efficacy signals justifying their further clinical testing in studies with rigorous clinical design. Cardiosphere based approach also is expanded to alloegeneic production avoiding the need of heart tissue sampling with limited quantity of starting material.

Orienting non-resident stem cells towards cardiogenesis would eliminate the need for the patient to undergo myocardial harvest (30, 31). Hallmark traits of cardiac development were successfully triggered within bone marrow-derived mesenchymal stem cells, establishing the first human scalable lineage-specified cardiopoietic phenotype derived without heart tissue harvest (34). Pre-clinical testing demonstrated that cardiac-specified progenitors reliably repair the failing myocardium, providing the foundation for clinical translation (31). The ensuing C-CURE clinical trial has been the first-in-man study to address the feasibility and safety of autologous bone marrow-derived cardiopoietic stem cell therapy, and assess efficacy signals in patients with ischemic cardiomyopathy (35). The successful completion of the study set the stepping stone for the currently ongoing CHART-1 trial to assess the efficacy of cardiopoietic cells in ischemic heart failure.

**Future trends.** At the core of upcoming practice, state-of-the-art regenerative principles are poised to increasingly leverage the understanding of multiplex parameters defining therapeutic outcome in the setting of the individualized heart failure management. Individualized medicine provides a powerful engine to tailor molecular profiles of patients in order to maximize therapeutic specificity, reduce treatment variability, and minimize adverse events (36). Insights in the regenerative basis of cell, tissue, and organ function and their interface with the environment will better define the disease risk, identify processes mediating disease susceptibility, or target mechanism-based therapies. The emerging field of regenerative medicine will thus grow in conjunction with the realization of the individualized medicine paradigm of “precision medicine” to create predictive, personalized and
preemptive solutions for tailored patient-specific strategies. Individualized treatment algorithms for regenerative medicine will require quantification of the inherent reparative potential to identify patients who would benefit from stem cell therapy. In this regard, systematic stratification of patients to match clinical traits and disease pathobiology with most adequate therapy will become integral in streamlining future evidence-based regenerative algorithms. To this end emphasis will be placed on delineating acute versus chronic disease substrates to ensure proper target strategy, timing and mode of intervention; separating ischemic versus non-ischemic conditions to guide focal versus diffuse therapy; preemptive management of co-morbidities and co-therapies to limit modifiable confounding factors to regenerative regimens. Moreover, recognizing key pharmacodynamics and pharmacokinetics features of regenerative biotherapeutics will aid in the design of next generation therapies. In this context, methods to enhance the biological propensity for repair are central in processes aimed at regenerative optimization. While first generation products consisted of purified, natural human cells typically used in their native state, second-generation cell products will refer to cells guided with growth factors or subpopulations selected based on tissue-specific biomarkers or genetically modified to direct cell differentiation, restrict tissue specification, and enhance the level of organ specificity. The goal with second generation cell products is to produce derivatives with enhanced safety and efficacy profiles compared to the original stem cell source. Third-generation products would serve to maximize therapeutic potential beyond that inherent to the original stem cell source or the respective derivatives (37). The goal with third-generation cell products would be for example also correction of genetic mutation or targeted therapy with recombinant protein, and/or engineered cell products with superior properties, such as enhanced stress tolerance and improved regenerative capacity. Engineered biomaterial scaffolds may help to overcome challenges currently attributed to cell retention or host tissue niche modification. Delivery of restorative exogenous signals through use of scaffolds, proteins, or microRNA aim may be applied to boost intrinsic repair function of the heart by modulating the interplay between reactive inflammatory response and stem cell recruitment into the ischemic tissue. In this regard, manipulation of the myocardial microenvironmental appears to boost the stem cell recruitment into the perivascular niche and enhance the efficacy of autologous stem cell delivery. Thus, synergy between optimizing cell products, delivery platforms and procedures will entail engineering
advanced methods to achieve increasingly uniform distribution of cells and limit early loss at time of administration. Ultimately, organ engineering based on decellularized matrix scaffolds and seizing the advances in the stem cell technology may provide a stepping stone for new frontier in tissue replacement (38, 39).

References

7. Malliaras K, Marbán E. Cardiac cell therapy: where we've been, where we are, and where we should be headed. Br Med Bull 2011; 98: 161-185.


3 Suppl 1: S78-82.


