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**Cardiac Resynchronization Therapy – New Concepts and
Techniques**

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1 INTRODUCTION

1.1 Definition and Aetiology of Heart Failure

Heart failure (HF) is a clinical syndrome associated with progressive structural and/or functional impairment of the heart, in which the myocardium is unable to provide cardiac output sufficient to meet the metabolic demands of the body. It represents a highly prevalent condition associated with poor prognosis. In Europe, approximately 15 million individuals are affected by HF, with a one-year mortality rate of 30–40%, approaching or even exceeding the mortality observed in several malignant diseases.

From an aetiological perspective, three principal categories of HF can be distinguished. The first and most common group includes conditions associated with primary myocardial damage. These encompass ischaemic heart disease as well as primary cardiomyopathies with a genetic background. Less frequently, toxic injury, immune-mediated processes, infiltrative diseases, and metabolic disorders may also contribute to the development of HF. The second category includes heart HF resulting from abnormal ventricular filling conditions. The most common underlying causes are arterial hypertension, advanced stages of structural valvular disease, pericardial and endomyocardial disorders, as well as high cardiac output states such as anaemia or thyrotoxicosis. The third aetiological group comprises cardiac arrhythmias, particularly persistent tachyarrhythmias and bradyarrhythmias. Of particular importance is the close association between atrial fibrillation (AF) and heart HF. Approximately one-third of patients with AF develop HF, while AF is present in roughly one-third of patients with established HF.

1.2 Classification of HF

HF can be classified according to several criteria. Based on temporal course, acute and chronic forms can be distinguished. However, even patients with chronic HF may experience sudden clinical deterioration in the form of acute decompensation.

In clinical practice, classification based on left ventricular (LV) ejection fraction (EF) plays a central role. This approach distinguishes four main patient groups.

- In case of heart failure with reduced ejection fraction (HFrEF), symptoms of HF are associated with markedly reduced LV systolic function, defined as an EF <40%.
- Patients with heart failure with mildly reduced ejection fraction (HFmrEF) have an EF between 41% and 49%.

- In heart HF with preserved ejection fraction (HFpEF), symptoms occur despite a preserved LV EF ($\geq 50\%$).
- A recently recognised category is HF with improved ejection fraction (HFimpEF). This group includes patients in whom a previously reduced EF ($<40\%$) improves by at least 10 percentage points and rises above 40% during follow-up.

Importantly, HFimpEF should still be regarded as a form of HFrEF from a therapeutic standpoint rather than as “resolved” heart failure, and continuation of guideline-directed medical and device therapy remains indicated.

1.3 Device Therapy in Chronic Heart Failure

If the clinical symptoms of HF persist for more than three months despite contemporary, guideline-directed medical therapy and without objective improvement in LV systolic function, consideration of device-based therapeutic interventions is warranted as the next step in management. Sudden cardiac death in patients with HF is frequently caused by malignant ventricular arrhythmias, and the implantation of an implantable cardioverter-defibrillator (ICD) plays a central role in their primary prevention. In HFrEF with narrow QRS complex — typically defined as a QRS duration below 130 ms — ICD therapy is generally considered as a standalone device therapy. In contrast, in the presence of a widened QRS complex, cardiac resynchronization therapy (CRT) becomes the preferred therapeutic approach.

The primary objective of CRT is the correction of ventricular electrical and mechanical dyssynchrony. Traditionally, this has been achieved through biventricular pacing; however, in recent years increasing attention has been directed toward conduction system pacing (CSP) as an alternative resynchronization strategy. Consequently, CRT can currently be implemented through two principal device-based approaches: conventional biventricular stimulation or direct stimulation of the His–Purkinje conduction system via CSP. Nevertheless, the majority of large-scale randomized clinical trials demonstrating the clinical benefits of CRT have been conducted using conventional biventricular pacing, whereas the evidence base supporting CSP remains comparatively limited. Accordingly, this section primarily focuses on the indications for conventional biventricular CRT in patients with sinus rhythm and AF.

In patients with sinus rhythm, the strongest indication for CRT (Class I recommendation) is the presence of persistent HF symptoms despite at least three months of optimized guideline-directed medical therapy, a LV EF below 35%, and a QRS duration exceeding 150 ms with left bundle branch block (LBBB) morphology. CRT is also

recommended in cases where the QRS duration ranges between 130 and 150 ms in the presence of LBBB morphology, or when the QRS duration exceeds 150 ms with non-LBBB morphology. In these clinical scenarios, the available evidence suggests that the expected clinical benefits outweigh the potential risks of the intervention; therefore, CRT implantation is assigned a Class IIa recommendation. In contrast, when a QRS duration of 130–150 ms is accompanied by non-LBBB morphology, the evidence supporting CRT efficacy is less robust. In this patient population, the clinical benefit of resynchronization therapy is less clearly established; therefore, implantation should be considered on an individual basis and carries a Class IIb recommendation.

In the presence of AF, the recommendations for CRT are largely based on similar clinical and echocardiographic criteria as those applied in patients with sinus rhythm. However, in this setting the effectiveness of electrical and mechanical resynchronization is strongly influenced by the proportion of ventricular pacing achieved. CRT should primarily be considered (Class IIa recommendation) in patients who continue to exhibit HF symptoms despite at least three months of optimized medical therapy, with an LV EF below 35% and a widened QRS complex (>130 ms). In this population, the clinical efficacy of CRT depends on achieving a high — preferably near 100% — rate of biventricular pacing. Ensuring such a high pacing proportion may require aggressive rate-control strategies and, when necessary, atrioventricular (AV) node ablation.

1.4 Mechanisms of Electromechanical Dyssynchrony in Wide QRS Complexes

1.4.1 Electrophysiological Characteristics of Typical LBBB

Intraventricular conduction disturbances associated with wide QRS complexes represent a heterogeneous group of electrocardiographic and electrophysiological abnormalities. Within this population, true LBBB — as defined by the Strauss criteria — can be distinguished from other non-LBBB conduction patterns.

The principal electrocardiographic criteria for true LBBB include:

- QRS duration >140 ms in men and >130 ms in women
- an rS or QS morphology in lead V1, indicating predominantly negative deflection
- mid-QRS notching or slurring in at least two of the following leads: I, aVL, V5, or V6

In typical LBBB, electrical activation begins in the RV because conduction through the left bundle branch is interrupted. The depolarisation wavefront then spreads slowly across the interventricular septum towards the LV via cell-to-cell myocardial conduction, eventually

reaching the lateral LV wall. This pattern results in right-to-left electrical dyssynchrony. As a consequence, the interventricular septum and anterior LV walls activate early, whereas the lateral and posterolateral LV walls activate with substantial delay. This temporal disparity between LV segments forms the electrophysiological basis of intraventricular mechanical dyssynchrony. The mechanical interaction between early septal contraction and delayed lateral wall activation produces a characteristic paradoxical septal motion pattern. At the onset of systole, the septum moves toward the LV cavity, followed by a recoil movement once the delayed lateral wall contraction occurs. This phenomenon is commonly described as „septal flash”, followed by elastic recoil. The asynchronous contraction pattern is also reflected in the motion of the cardiac apex. During systole, the apex exhibits a characteristic oscillatory motion known as apical rocking. From an energetic standpoint, the early septal contraction is inefficient because it occurs before a significant rise in LV pressure has developed. In contrast, contraction of the lateral wall occurs when LV pressure is already elevated, making it mechanically more effective but energetically inefficient due to additional energy loss. As a result, the LV pressure–volume relationship becomes unfavourable, systolic efficiency decreases, and mitral valve closure may become asynchronous. This process can lead to functional mitral regurgitation, which further worsens haemodynamic status. Over time, persistent mechanical dyssynchrony promotes progressive LV remodelling, increases wall stress, and contributes to the progression of HF. CRT using biventricular pacing can reorganise the spatial and temporal sequence of ventricular activation, thereby reducing transseptal conduction delay and homogenising LV activation. Electrical resynchronisation is often reflected by shortening of the QRS complex and changes in QRS morphology, which correlate with improvement in mechanical synchrony and the development of reverse LV remodelling. Both experimental and clinical data consistently demonstrate that patients with true LBBB derive substantial haemodynamic and prognostic benefit from CRT. However, even within the LBBB population, significant heterogeneity exists in activation patterns, which partly explains the variability in therapeutic response and highlights the importance of patient-specific pacing strategies.

1.4.2 Electrophysiological Characteristics of Non-LBBB Morphology

A wide QRS complex with non-LBBB morphology cannot be characterized using the Strauss criteria. Intraventricular conduction delay (IVCD), resulting from damage to the distal conduction system, often does not lead to pronounced delayed activation of the LV lateral wall. Instead, it typically reflects a more complex conduction disturbance frequently involving multiple fascicles, which limits the degree of electrical resynchronization that can be achieved

with CRT. Subgroup analyses of the MADIT-CRT trial demonstrated that, in patients with non-LBBB QRS morphology, the overall effect of CRT is less favorable compared with those exhibiting true LBBB. At the same time, the analyses revealed that prolongation of the PR interval (first-degree AV-block) significantly modifies therapeutic response. Within the subgroup of patients with non-LBBB morphology and markedly prolonged PR interval, CRT-D therapy significantly reduced the risk of HF events and composite clinical outcomes compared with ICD therapy alone. In contrast, in patients with non-LBBB morphology and shorter PR intervals, no clinical benefit of CRT could be demonstrated. These findings suggest that the non-LBBB population is electrophysiologically heterogeneous and that response to CRT is determined not only by QRS morphology but also by the degree of AV conduction delay. The results of recent meta-analyses further indicate that in patients with non-LBBB QRS morphology, meaningful clinical benefit is generally observed only in the presence of markedly prolonged QRS duration (>150 ms).

In addition to IVCD, the non-LBBB category also includes typical right bundle branch block (RBBB), whose pathophysiology is primarily characterized by delayed conduction within the RV, while LV activation remains preserved in most cases. Electrophysiological mapping studies have demonstrated that during RBBB ventricular electrical propagation occurs slowly, predominantly via cell-to-cell conduction. Activation first appears in the LV septal region and subsequently spreads to the RV with significant delay, with the RV lateral wall and outflow tract representing the latest activated regions. Consequently, the RV endocardial depolarization time is markedly prolonged, and QRS widening primarily reflects delayed activation of the RV free wall and outflow tract. This mechanism differs fundamentally from the pathological right-to-left activation pattern observed in LBBB, which is characterized by pronounced dyssynchrony between the LV septum and the lateral wall. On the surface electrocardiogram, typical RBBB morphology is characterized by a broad terminal S wave in leads I and aVL and an rsR' or rSR' pattern in lead V1. In contrast, in non-classical RBBB the S wave may be absent in the lateral leads, and the ECG frequently shows left axis deviation and/or PR prolongation, suggesting that, in addition to the RBBB, the left-sided conduction system is also involved. In such cases, the limb leads may resemble LBBB morphology, a phenomenon often referred to as “masked” LBBB. This pattern is typically associated with advanced ischemic cardiomyopathy and extensive myocardial scarring. These patients may exhibit particularly favorable responses to CRT delivered via biventricular pacing; however, the misleading ECG appearance may lead to underrecognition of CRT indications if the underlying LV activation abnormality is not identified.

In 30–50% of patients with HF and typical RBBB morphology on the surface ECG, significant LV mechanical dyssynchrony may also develop, which may manifest as interventricular dyssynchrony, intraventricular dyssynchrony, or a combination of both. Several interrelated mechanisms may contribute to this phenomenon. On the one hand, delayed RV activation may secondarily influence the timing of LV contraction through its effect on interventricular septal motion. On the other hand, in the presence of structural heart disease — either ischemic or non-ischemic cardiomyopathy — LV conduction slowing is frequently present due to fascicular or more distal impairment of the LV conduction system. However, experimental and clinical studies suggest that in isolated typical RBBB the LV pump function is less affected by the conduction abnormality itself than in LBBB, as the degree of electromechanical dyssynchrony is generally smaller or may even be absent. Biventricular pacing, however, produces a non-physiological activation sequence because stimulation of the LV lateral wall from the epicardial surface results in cell-to-cell propagation from epicardium toward endocardium. While this activation pattern can effectively reduce the pronounced septal–lateral dyssynchrony observed in LBBB, its hemodynamic benefit is limited in RBBB due to the smaller baseline dyssynchrony and, in certain cases, may even introduce additional dyssynchrony. For these pathophysiological reasons, the conventional implementation of CRT may not be optimal in this patient population. Large registry studies and meta-analyses have demonstrated that in patients with RBBB the mortality rate and progression of HF following CRT are less favorable compared with those observed in LBBB. The absence of clinical benefit is particularly evident in patients in whom substantial LV electrical and/or mechanical dyssynchrony cannot be demonstrated. In RBBB, the potential benefit of CRT may primarily relate to modest improvement in RV function and ventricular interdependence, whereas its potential drawback lies in iatrogenic prolongation of LV activation and the associated risk of adverse hemodynamic effects. Overall, based on current evidence, isolated RBBB cannot be considered an optimal indication for conventional CRT; however, in carefully selected patient populations and with individualized pacing strategies, the role of CRT in this setting warrants further investigation.

1.5 Clinical Effects of CRT and Assessment of CRT Response

The beneficial effects of CRT are primarily mediated through the restoration of electromechanical synchrony within the heart. CRT favourably influences synchronisation at multiple levels, including interventricular synchrony between the RV and LV, intraventricular synchrony between individual segments of the LV and AV synchrony between

atrial contraction and ventricular filling. The combined effect of these mechanisms results in the haemodynamic improvements observed following CRT.

1.5.1 Assessment of Therapeutic Response to CRT

Approximately one third of patients undergoing CRT implantation do not demonstrate improvement in echocardiographic parameters, clinical symptoms of HF, or long-term outcomes following therapy. These patients are conventionally referred to as CRT non-responders. However, the traditional definition of therapeutic response to CRT remains inconsistent, resulting in considerable variability in the reported proportions of responders and non-responders. Different clinical studies have applied heterogeneous endpoints and assessment methods, which complicates direct comparison of results across studies.

For this reason, most studies define CRT response primarily on the basis of objective echocardiographic indicators of LV reverse remodeling. The most frequently applied criteria include an increase in LV EF of at least 5–10% and/or a reduction in LV end-systolic volume index (ESVi) of 10–15% during a follow-up period of 6–12 months; in some studies these two parameters are used in combination. Reverse remodeling-based criteria demonstrate a closer association with survival and reduced hospitalization for HF, as they reflect favorable structural and functional changes in LV geometry that are strongly linked to long-term prognosis. Using these criteria, the proportion of non-responders typically ranges between 30% and 45%. Importantly, the absence of reverse remodeling does not necessarily indicate the complete lack of clinical benefit, as the relationship between symptomatic improvement and structural cardiac changes is not always linear.

Another approach to defining response is based on improvement in clinical status. This includes changes in the New York Heart Association (NYHA) functional class, improvement in exercise capacity assessed by the six-minute walk test, and better scores on quality-of-life questionnaires such as the Minnesota Living with Heart Failure Questionnaire. However, these clinical parameters inherently contain subjective components and show only weak-to-moderate correlation with long-term prognosis. In some studies, a combined clinical response has been defined as either an improvement of at least one NYHA functional class or a $\geq 15\%$ increase in performance on the six-minute walk test. When response criteria are based on clinical status, the proportion of non-responders is generally lower than when reverse remodeling-based definitions are applied. An additional limitation of these endpoints is their susceptibility to placebo effects, patient perception, and potential biases related to the clinical trial environment.

In certain investigations, the effectiveness of CRT has been defined using outcome-based endpoints such as mortality, morbidity, or reduction in hospitalizations due to HF. These endpoints are particularly suitable for assessing CRT efficacy in large-scale clinical trials. However, event-based endpoints are difficult to apply at the individual patient level because clear pre- and post-intervention comparisons are often not feasible. Furthermore, all-cause mortality may include events that are not directly related to the mechanisms of action of CRT. Hospitalization endpoints are more closely related to the progression of HF but may also be influenced by clinical decision-making and healthcare system factors. When such criteria are applied, the proportion of non-responders generally falls between those defined by functional and reverse remodeling-based criteria, with substantial heterogeneity between studies.

To overcome the limitations associated with the use of individual endpoints, clinical composite scoring systems have been introduced, integrating functional status, quality of life, reverse remodeling, and clinical events into a single evaluative framework. The aim of this approach is to establish an integrated and clinically meaningful endpoint that simultaneously reflects mortality, morbidity, and changes in functional capacity. One of the most widely used examples is the Packer clinical composite score, which incorporates mortality, hospitalization due to HF, and changes in functional status. This system categorizes patients into three groups: improved, unchanged, and worsened clinical status. The worsened category includes all patients who experience death from any cause, hospitalization due to HF, or require intensification of therapy because of clinical deterioration during the follow-up period. An improved status requires the absence of mortality and hospitalization and, in addition, evidence of either improvement by at least one NYHA functional class or favorable patient self-assessment. Patients who do not meet the criteria for either improvement or worsening are classified as unchanged. The hierarchical structure of this scoring system ensures that major clinical events take precedence over functional parameters in determining overall outcome.

1.5.2 New definition of CRT response

The Packer clinical composite score has been applied in several landmark CRT trials, including COMPANION, CARE-HF, and MIRACLE. The REVERSE study is of particular importance in this context, as it evaluated the effects of CRT in patients with milder symptoms (NYHA class I–II) and employed the Packer clinical composite score as its primary endpoint. The study is considered a milestone not only for this reason but also because it recognized disease stabilization — defined as the absence of clinical deterioration following CRT — as a favorable therapeutic outcome. Structural improvement does not necessarily translate into

substantial symptomatic or functional improvement in every case. Moreover, given the progressive nature of HF, the clinical benefit of CRT may manifest not only as overt improvement but also as the stabilization or slowing of disease progression. Consequently, the traditional dichotomous classification of patients into responders and non-responders has increasingly been questioned in recent years.

Based on these considerations, Steffel and Ruschitzka proposed a more comprehensive classification of CRT response. This framework distinguishes two categories of clinical improvement (responders and super-responders), two forms of clinical deterioration (non-responders and negative responders), as well as a stable patient group referred to as non-progressors. The prognosis of non-progressors proved to be more favorable in the short and intermediate term than that of negative responders (progressors), even in the absence of significant reverse remodeling. The heterogeneity of the responder population is further emphasized by the identification of super-responders, in whom LV function improves to near-physiological levels.

1.6 Conduction System Pacing as a New Direction in Cardiac Pacing Therapy

1.6.1 Definition and Types of Conduction System Pacing

CSP represents one of the most significant paradigm shifts in pacemaker therapy. The aim of this technique is the direct activation of the heart's intrinsic conduction system, whereby ventricular depolarisation occurs through the physiological His–Purkinje network rather than via the slowly conducting working myocardial fibres. CSP emerged from the pathophysiological recognition of electromechanical dyssynchrony induced by conventional RV pacing, in which depolarisation spreads through the myocardium in a cell-to-cell manner. This results in a wide QRS complex, intra- and interventricular dyssynchrony, and, over the long term, LV remodelling and pacemaker-induced cardiomyopathy. In parallel, conventional biventricular CRT does not invariably ensure complete electrical and mechanical synchrony. This limitation is partly attributable to differences between epicardial and endocardial activation patterns, and partly to the presence of myocardial scar tissue and anatomical constraints, which may explain the relatively high proportion of patients who do not respond adequately to conventional CRT therapy. Owing to these limitations, CSP is increasingly utilised in contemporary practice as an alternative to conventional single- or dual-chamber pacemaker therapy in bradycardia indications, and in selected cases as an alternative to biventricular pacing-based CRT.

CSP is generic term encompassing His bundle pacing (HBP) and left bundle branch area pacing (LBBAP). The shared objective of these two strategies is the direct activation of the His–Purkinje conduction system, thereby preserving or restoring the physiological pattern of ventricular depolarisation. From an anatomical and electrophysiological perspective, however, important differences exist between them. HBP involves direct stimulation of the most proximal, common segment of the conduction system. Its theoretical advantage lies in the activation of the His bundle, which allows antegrade conduction through both the right and left bundle branches and their distal fascicles along the native conduction pathways. Electrophysiologically, selective and non-selective HBP can be distinguished. In selective stimulation, only the His bundle is captured, which on the surface ECG is characterised by an isoelectric interval following the pacing artefact and a QRS morphology similar to the native complex. In non-selective pacing, depolarisation involves both the His bundle and the adjacent septal myocardium; consequently, the initial portion of the QRS complex exhibits a fusion pattern, whereas the later portion reflects activation through the specialised conduction system. Clinical studies have demonstrated that both forms are capable of reducing QRS duration, attenuating electromechanical dyssynchrony, and improving or preserving LV function in selected patient populations.

LBBAP refers to stimulation of conduction system structures located distal to the His bundle. The term “area pacing” reflects the fact that selective stimulation of the main trunk of the left bundle branch is not achieved in every case; rather, the concept encompasses the proximal segment of the left bundle, its fascicular branches, and the subendocardial region of the LV septum. Accordingly, three principal forms of LBBAP can be distinguished. In left bundle branch pacing (LBBP), the electrophysiological criteria described later confirm direct stimulation of the left bundle branch, typically resulting in a relatively narrow QRS complex with an RBBB morphology. In left fascicular pacing (LFP), direct electrical activation of either the anterior or posterior fascicle is achieved. In left ventricular septal pacing (LVSP), the lead is positioned within the LV endocardial portion of the interventricular septum, providing relatively physiological LV activation through engagement of the distal Purkinje network without direct stimulation of the left bundle branch.

One of the most important differences between HBP and LBBAP lies in their technical and electrical characteristics. The His region is an anatomically small structure located within the fibrous membranous septum, and its precise localisation represents a technical challenge. This is reflected in longer fluoroscopy and procedure times, as well as a higher incidence of elevated pacing thresholds, lower R-wave amplitudes, and long-term threshold increases with

HBP. In patients with AV-block who are pacemaker-dependent, the implantation of a backup ventricular lead may therefore be considered. In contrast, during LBBAP the pacing lead is deeply anchored within the muscular portion of the septum, providing a more stable position, lower and more durable pacing thresholds, and larger sensed intracardiac signals. Furthermore, compared with HBP, LBBAP is associated with a more favourable learning curve, as the anatomical target area is larger and technically more accessible. Consequently, procedural acquisition is generally faster, overall procedure duration shorter, and fluoroscopy time lower compared with HBP.

1.6.2 Indications for CSP

Current European guidelines still considerably restrict the indications for CSP, nevertheless, they clearly acknowledge its clinical relevance. HBP carries a Class IIa recommendation for patients requiring CRT in whom implantation of a LV lead via the coronary sinus has been unsuccessful. HBP is also listed with a Class IIb recommendation in the context of AV node ablation performed for supraventricular arrhythmias — most commonly AF — provided that the baseline QRS complex is narrow. In patients with preserved LV function who require pacemaker therapy for bradycardia, current guidelines continue to regard conventional RV endocardial pacing as the primary strategy. Similarly, in patients with HF who have an indication for resynchronisation therapy, biventricular pacing remains the preferred standard treatment, largely owing to the predominance of evidence derived from large-scale randomised clinical trials. The current European pacemaker guideline does not provide a formal recommendation regarding LBBAP because of the limited clinical evidence available for this technique.

The 2023 consensus statement from the United States, developed by the Heart Rhythm Society (HRS) in collaboration with the Asia Pacific Heart Rhythm Society (APHRS) and the Latin American Heart Rhythm Society (LAHRS), with the professional endorsement of the American Heart Association (AHA), introduces a new conceptual framework for conduction system stimulation. The document adopts the concept of physiological pacing, defined as any pacing strategy aimed at preserving or restoring ventricular synchrony. Within this framework, the term encompasses both conventional CRT achieved through LV stimulation and conduction system pacing techniques such as HBP and LBBAP. The primary objective of this recommendation is therefore not merely the introduction of a new technical approach into clinical practice but rather the promotion of a more physiological strategy for ventricular activation. The guideline discusses the role of physiological pacing in detail in two

principal clinical settings: the treatment of bradycardia and CRT indications. Regarding bradycardia management, the document emphasises that in patients expected to require a high proportion of ventricular pacing — such as those with complete or high-grade AV block — conventional RV pacing may lead to LV dysfunction over the long term. In this context, physiological pacing should be considered as a strategy to prevent pacing-induced ventricular dysfunction. LBBAP may be particularly advantageous, as it is capable of providing a more physiological pattern of ventricular activation while maintaining stable electrical parameters. In the field of CRT indications, the consensus statement reflects a significant conceptual shift compared with earlier European guideline documents. Although implantation of a conventional biventricular pacemaker remains the first-line treatment in patients with HFrEF and LBBB QRS morphology, the document clearly states that when conventional CRT is technically infeasible or fails to achieve adequate electrical correction, CSP represents a reasonable and recommended alternative. This is particularly relevant in situations where implantation of an LV lead via the coronary sinus is unsuccessful, or when the clinical or electrical response to CRT is inadequate. Furthermore, the expert consensus does not consider physiological pacing solely as a “rescue” therapy. In patients requiring resynchronisation, CSP may also be considered (Class IIb recommendation) as an alternative to conventional CRT in the presence of wide QRS complexes (>150 ms) with either LBBB or non-LBBB morphology.

1.6.3 Application of CSP in RBBB

Although current professional guidelines recommend CRT with a Class IIa indication for QRS duration >150 ms and Class IIb for 130–150 ms in patients with RBBB and HFrEF within the non-LBBB ECG morphology group, the efficacy of biventricular pacing in this patient population remains limited. Both clinical trials and registry data consistently demonstrate that the therapeutic response in this cohort is heterogeneous and overall modest. Functional improvement — such as favourable changes in New York Heart Association (NYHA) functional class or increased exercise capacity — is observed less frequently, while echocardiographic parameters, particularly LV EF and the extent of reverse remodelling, also tend to show more modest improvement. The overall responder rate is low, and a non-negligible proportion of patients exhibit neither structural nor clinical benefit. Moreover, in certain subgroups, less favourable outcomes than anticipated cannot be excluded, including increased rates of hospitalisation or even adverse effects on mortality.

Under these circumstances, CSP has emerged as a potential therapeutic approach in RBBB, similarly to its application in LBBB, aiming to restore a physiological pattern of ventricular depolarisation through direct activation of the His–Purkinje network.

The clinical development of CSP in RBBB initially began with HBP. Early multicentre experiences demonstrated that permanent HBP can be successfully implemented in patients with HFrEF and RBBB with a high procedural success rate, frequently resulting in a significant reduction in QRS duration. Electrical resynchronisation was accompanied by echocardiographic improvement, including increased LV EF, evidence of reverse remodelling, and improvement in patients' functional status. These findings provided the first proof that meaningful electromechanical resynchronisation could be achieved in RBBB using CSP. Subsequently, LBBAP emerged as an alternative physiological pacing strategy. In larger international studies involving patients with RBBB and reduced LV EF, LBBAP demonstrated a higher implantation success rate than HBP while maintaining stable and low pacing thresholds. The therapy resulted in reductions in QRS duration comparable to those observed with HBP, accompanied by improvement in LV EF and favourable clinical and echocardiographic response rates. Although long-term, large-scale randomised trials remain limited, the currently available evidence suggests that CSP represents a clinically promising alternative to conventional biventricular CRT in patients with RBBB.

1.7 New echocardiographic methods for the assessment of left ventricular function

1.7.1 Deformation echocardiography: global longitudinal strain (GLS) and its role in the assessment of LV function and response to CRT

A more accurate method for the assessment of LV function than conventional echocardiographic techniques is two-dimensional speckle tracking echocardiography (2D-STE), one of whose key parameters is the determination of global longitudinal strain (GLS). Two-dimensional speckle tracking echocardiography is a deformation imaging technique based on two-dimensional ultrasound acquisition that tracks the natural acoustic patterns (“speckles”) visible within the myocardium on ultrasound images from frame to frame. These small, unique patterns are linked to specific regions of the myocardium, allowing their motion and deformation to be quantitatively analysed using computer-based algorithms. This method enables objective measurement of myocardial longitudinal, circumferential and radial shortening (strain), as well as their temporal characteristics, independently of the direction of the ultrasound beam. GLS represents the aggregated measure of segmental longitudinal

deformation obtained through speckle tracking analysis. A major advantage of this technique is that it detects subclinical systolic dysfunction more sensitively than LV EF, while also demonstrating better reproducibility and reduced dependence on loading conditions such as preload and afterload. Furthermore, it more accurately reflects the function of subendocardial myocardial fibres and is therefore capable of identifying functional deterioration at an earlier stage. Nevertheless, GLS is not entirely load-independent; its values may be influenced by blood pressure, image quality and inter-vendor variability, which may limit the uniform application of absolute cut-off values. For the assessment of GLS, the LV is divided into segments using standard apical views (four-chamber, two-chamber and three-chamber views). The maximal longitudinal shortening of each segment during systole is determined, and the global value is calculated as the average of these measurements. GLS therefore characterises the overall longitudinal contractile performance of the LV and is expressed as a negative percentage value. Deformation parameters provide additional value in both the evaluation and prediction of therapeutic response to CRT. On the one hand, changes in GLS measured at baseline and following therapy may sensitively reflect functional improvement even in cases where LV EF shows only minimal change. On the other hand, analysis of the temporal characteristics of segmental strain curves allows quantitative assessment of mechanical dyssynchrony, thereby enabling the identification of patients in whom significant baseline LV dyssynchrony suggests a favourable response to CRT. The same method also remains informative after the intervention, as the presence of substantial residual dyssynchrony may explain the absence of, or an inadequate, therapeutic response.

1.7.2 Echocardiographic assessment of myocardial work and its role in cardiac resynchronisation therapy

Further development of strain-based assessment is the echocardiographic estimation of myocardial work, the principle of which is the combination of the temporal course of LV deformation with a LV pressure curve derived from peripheral cuff blood pressure, thereby constructing a so-called pressure-strain loop. This approach provides not only information about the magnitude of myocardial shortening but also an approximation of the loading conditions under which contraction occurs. The method allows overall mechanical performance to be separated into clinically interpretable components, including constructive work, wasted work resulting from discoordinated contraction, and mechanical efficiency derived from the ratio of these parameters. This approach is particularly advantageous in HF because it is less

sensitive to loading conditions and therefore helps differentiate whether a reduction in GLS reflects impaired contractility or is primarily related to increased afterload, thereby offering a more refined haemodynamic interpretation than conventional volume-based parameters. The role of myocardial work in CRT is of particular importance because it attempts to capture directly the energetic consequences of ventricular dyssynchrony. The discoordinated contraction associated with LBBB typically results in substantial energy loss, as certain myocardial segments perform work at a time or in a direction that does not contribute to effective ejection and may even oppose it mechanically. One of the principal effects of CRT is therefore not necessarily an immediate and marked improvement in global LV function, but rather the reduction of this internal energy loss and the redirection of myocardial work towards effective ejection. Indices of myocardial work may therefore be useful in several aspects of CRT: before the intervention they may help identify patients with a significant degree of energetically inefficient dyssynchrony, after device implantation they may provide objective feedback regarding whether wasted work has been reduced and whether mechanical efficiency has improved, and they may also assist in patient selection in groups where the likelihood of response to resynchronisation therapy is less predictable based on conventional markers alone, such as in patients with non-left bundle branch block QRS morphology. From a clinical perspective, this approach interprets the effects of resynchronisation therapy not primarily in terms of volumetric improvement but rather through the concept of mechanical efficiency, which more closely reflects the underlying pathophysiology of ventricular dyssynchrony.

2 OBJECTIVES

The clinical impact and long-term prognostic significance of device-based resynchronisation therapies in HF remain complex issues, particularly because of the substantial heterogeneity in therapeutic response. The aim of the present thesis was, on the one hand, to approach the effectiveness of resynchronisation therapy from a novel perspective through a comprehensive evaluation of the response to CRT based on both structural and clinical parameters. In parallel, we investigated the electrophysiological, mechanical and clinical effects of CSP and examined how these changes may be integrated into a broader interpretation of the effectiveness of resynchronisation therapy.

In the first part of the study, we examined how the prognosis of patients undergoing CRT-D implantation may be evaluated using a progressor–non-progressor–responder framework rather than the conventional responder–non-responder dichotomy. Although this classification is primarily based on structural LV changes, the dynamics of reverse remodelling

parameters and clinical status do not always coincide. Accordingly, our aim was to develop an evaluation framework that integrates variables of reverse remodelling with clinical events, including hospitalisation for HF and/or malignant ventricular arrhythmias, thereby enabling a more accurate prediction of long-term outcomes through the combined assessment of structural and clinical parameters.

In the second part of the study, we evaluated the effects of CSP in patients with HF and RBBB QRS morphology, as the expected efficacy of conventional CRT is less favourable in this population, thereby justifying the investigation of alternative resynchronisation strategies. In this cohort, the complex electrophysiological and mechanical effects of CSP were analysed in relation to clinical outcomes, with particular emphasis on changes in LV function, deformation parameters and myocardial work. Our objective was not to demonstrate the superiority of CSP over biventricular pacing, but rather to explore the complex structural, mechanical and clinical changes induced by conduction system pacing in this specific population and to assess how these factors contribute to a comprehensive evaluation of patient status.

3 METHODS AND PATIENT SELECTION

3.1 Study concept and overall study design

The PhD research was based on two conceptually complementary single-centre retrospective studies aimed at evaluating electrical resynchronisation strategies applied HFrEF. The first investigation focused on redefining and refining the prognostic evaluation of therapeutic response following conventional CRT performed with biventricular pacing. This approach was based on the combined consideration of structural reverse remodelling and early clinical events, allowing the traditional responder–non-responder dichotomy to be surpassed and enabling a more comprehensive interpretation of disease progression modification. The second study evaluated the applicability and effects of conduction system pacing in a patient population in which conventional CRT cannot be considered the optimal resynchronisation strategy. Our aim was to analyse the clinical and functional consequences of an approach based on physiological impulse conduction. Both studies were approved by the Scientific and Research Ethics Committee of the University of Debrecen (approval number: BMEÜ/4388-1/2022/EKU) and were conducted in accordance with the principles of the Declaration of Helsinki.

3.2 Evaluation of therapeutic response to CRT performed with biventricular pacing

In the first part of our study, patients were included who underwent de novo CRT-D implantation between 1 January 2010 and 31 December 2019 according to standard CRT indications. Patients were eligible if at least 12 months of survival and documented follow-up were available. The indications for CRT-D implantation were consistent with the contemporary European guidelines, and the choice of a defibrillator-equipped device was based on the need for primary or secondary prevention of malignant ventricular arrhythmias. All patients received optimised medical therapy (OMT) according to current professional recommendations both before and after the intervention. Follow-up was performed according to a structured protocol, with visits scheduled at 6 weeks, 6 months and 12 months after implantation, and subsequently every 6–12 months. At each visit a 12-lead ECG, device interrogation, assessment of NYHA functional class and echocardiographic examination were performed. During echocardiography, atrial and ventricular dimensions were assessed, valvular abnormalities were quantified and LV EF was measured using the Simpson biplane method. Baseline patient characteristics included demographic data (age and sex), cardiac functional parameters (pre- and postoperative LV EF and NYHA functional class), electrocardiographic characteristics (QRS duration and morphology), body mass index (BMI), HF aetiology, comorbidities (hypertension, diabetes mellitus, AF, stroke or transient ischaemic attack), and major laboratory parameters (serum creatinine and haemoglobin levels). During the first year after implantation, hospitalisation for acute HF and the occurrence of sustained ventricular arrhythmias detected by the device were documented. Long-term outcomes were evaluated based on all-cause mortality, heart transplantation or the need for mechanical circulatory support (LV assist device, LVAD), which were considered the primary endpoint of the study. The evaluation of response to CRT was based on the change in LV EF observed on echocardiography performed at the 12-month follow-up visit after implantation. Accordingly, patients were classified into three main groups:

- Responders were defined as those with an improvement in LV EF of at least 10%
- The non-progressor group included patients with an improvement between 0% and 10%
- Progressor population consisted of patients in whom LV EF decreased.

Subsequently, each of these three groups was further stratified according to the occurrence of early clinical events within the first year after implantation, including hospitalisation for acute heart failure and/or sustained ventricular arrhythmias requiring ICD therapy. Based on the

combination of structural response and early clinical events, the entire cohort was categorised into three new prognostic groups described as improving, stabilising and worsening, allowing a more comprehensive interpretation of the therapeutic effect that better reflects the clinical course.

3.3 Application of conduction system pacing in HFrEF with RBBB

The heterogeneity of response to CRT highlights the importance of investigating alternative resynchronisation strategies in patient groups in whom the expected effectiveness of conventional biventricular CRT is limited. Accordingly, in the second part of our study we evaluated the clinical and echocardiographic effects of CSP performed for resynchronisation indications in patients with HFrEF and right bundle branch block QRS morphology. The study was a retrospective observational analysis including consecutive patients treated between January 2021 and January 2024 who had a QRS duration ≥ 130 ms with RBBB ECG morphology, LV EF $< 35\%$, and NYHA functional class II–IVa despite at least six months of guideline-directed OMT including β -blockers, mineralocorticoid receptor antagonists, ACE inhibitors or ARB or ARNI, and SGLT2 inhibitors. Patients with advanced AV conduction disturbances requiring pacemaker implantation for bradycardia indications were excluded. During CSP implantation, HPB was initially attempted and in cases of unsuccessful implantation the strategy was converted to LBBAP; in the later phase of the study LBBAP became the first-line implantation technique. The procedures were performed using a Medtronic C315His delivery sheath and a SelectSecure 3830 active fixation lead. During HPB implantation the His bundle region was identified by unipolar mapping following tricuspid valve angiography using an electrophysiological recording system. After detection of the His potential, the lead was fixed by 4–6 clockwise rotations. The presence and type of His capture, including selective and non-selective HPB, as well as the pacing threshold required for RBBB correction, were determined by gradual reduction of pacing output starting from 5 V/0.4 ms. During LBBAP implantation the sheath and lead were positioned approximately 1–2 cm distal to the septal leaflet of the tricuspid valve on the RV septum in the direction of the apex, and the optimal implantation site was identified by unipolar pacing. The appropriate position was indicated by the characteristic QRS morphology observed in lead V1, typically a W configuration, together with discordant QRS patterns in leads aVR and aVL and in the inferior leads, particularly leads II and III. After identifying the optimal initial septal position, the lead was advanced into the interventricular septum by controlled rapid rotations. Adequate advancement was indicated by fixation beats with right bundle branch block morphology

observed during lead screwing, suggesting proximity to the conduction system structures. Once the desired depth was achieved, lead rotation was stopped and detailed electrophysiological verification was performed. This included assessment of the presence of left bundle branch or fascicular potentials, evaluation of the QRS morphology during unipolar pacing, measurement of myocardial injury current, and analysis of the electrical lead parameters. When programming the pacing mode, a unipolar configuration was primarily used. If correction of the right bundle branch block pattern was not satisfactory, bipolar pacing was also attempted with the inclusion of anodal capture to achieve further conduction system correction. During CSP the type of capture was determined according to previously published electrophysiological criteria. In HPB, selective capture was confirmed when an isoelectric interval was present between the pacing stimulus and the onset of the QRS complex, indicating pure conduction system activation, whereas non-selective HPB was characterised by the appearance of a pseudo-delta wave following the stimulus, reflecting simultaneous myocardial and conduction system activation. The procedure was considered unsuccessful if stable and reproducible His capture could not be achieved with an acceptable pacing threshold ($<3 \text{ V}/0.4 \text{ ms}$) or if partial or complete correction of the right bundle branch block pattern was not achieved. In the case of LBBAP, confirmation of conduction system activation required a right bundle branch block pattern in lead V1 during unipolar pacing together with at least one additional criterion: transition of QRS morphology during threshold testing from non-selective LBBP to selective LBBP or from non-selective LBBP to LVSP, or the presence of a left bundle branch or fascicular potential with a potential–V6 R-wave peak time identical to the stimulus–V6 R-wave peak time during pacing. If these criteria could not be clearly evaluated but a Qr or QR morphology appeared in lead V1, LVSP was diagnosed. The procedure was considered unsuccessful in cases of high pacing threshold, insufficient septal penetration, or if the above LBBAP criteria were not fulfilled.

3.4 Comprehensive assessment of LV function and mechanics using advanced echocardiographic methods

Detailed echocardiographic examinations were performed according to a standardised protocol prior to CSP implantation and at 6 months after the intervention. Image analysis was carried out in all cases by the same investigator who was blinded to the clinical data in order to minimise measurement bias. LV EF was determined using the modified Simpson method and LV volumes were indexed to body surface area. Echocardiographic response to CSP was defined as an increase in LV EF of at least 5% at the 6-month follow-up. In addition to

conventional volumetric parameters, deformation-based analysis using 2D speckle tracking echocardiography was performed to provide a more detailed characterisation of LV function, and GLS and peak strain dispersion (PSD) were determined. For PSD measurement, the time to peak longitudinal strain (time-to-peak strain) was determined in all 17 LV segments until aortic valve closure. PSD was calculated as the standard deviation of these values and therefore quantifies the temporal heterogeneity of segmental contraction and intraventricular mechanical dyssynchrony. To obtain a more comprehensive evaluation of myocardial performance, pressure–strain loop-based myocardial work analysis was also performed. This method integrates GLS data with non-invasively measured systolic blood pressure, allowing the assessment of contractility while accounting for the prevailing afterload. The global work index (GWI) represents the total mechanical work performed during systole, whereas global constructive work (GCW) reflects the effective work contributing to LV ejection and global wasted work (GWW) characterises energetically non-productive myocardial deformation. Global work efficiency (GWE) is calculated as the ratio of global constructive work to global work index (GWI) and can be interpreted as an integrated parameter of myocardial energy utilisation. The combined use of deformation and myocardial work parameters allowed the effects of CSP to be evaluated not only at the level of structural reverse remodelling but also in terms of mechanical synchronisation and energetic efficiency, considering the specific electromechanical characteristics of the HFrEF population with RBBB morphology.

3.5 Statistical analysis

Data analysis was performed using IBM SPSS Statistics and GraphPad Prism software. Continuous variables were expressed as mean $\pm$ standard deviation or mean $\pm$ standard error, while categorical variables were presented as absolute numbers and percentages. After assessment of distribution normality, comparisons between two independent groups were performed using the independent samples t-test for normally distributed variables and the Mann–Whitney test for non-normally distributed variables. Comparisons among three or more independent groups were performed using analysis of variance or, in the case of non-normal distribution, the Kruskal–Wallis test. Categorical variables were compared using the chi-square test. For comparison of baseline and follow-up parameters within the same patients, the paired t-test was applied for normally distributed variables and the Wilcoxon test for non-normally distributed variables. In the case of multiple comparisons, the Bonferroni–Holm (BH) correction was applied to reduce the risk of type I statistical error. Long-term clinical outcomes were analysed using Kaplan–Meier survival analysis, and differences between groups were

assessed with the log-rank test. Independent predictors of outcomes were identified using univariate and multivariate Cox proportional hazards regression models, allowing estimation of relative risk and corresponding confidence intervals. Statistical significance was defined as $p < 0.05$.

4 RESULTS

The results section of the present thesis summarises the findings of two conceptually related but analytically distinct studies addressing the prognostic and echocardiographic mechanical aspects of device-based therapy in HFrEF.

In the first part, the long-term outcomes of patients treated with CRT-D were analysed, with particular emphasis on the reinterpretation of the concept of non-response and the development of a prognostic framework integrating early clinical events. In the second part, the clinical and mechanical effects of CSP were evaluated in a population of patients with HFrEF and RBBB who fulfil conventional indications for CRT but are expected to derive limited benefit from biventricular pacing, with particular focus on changes in electrical resynchronisation, LV function and mechanical synchrony.

4.1 Long-term prognosis of CRT-D therapy and reinterpretation of the non-responder status in HFrEF

4.1.1 Clinical and demographic characteristics of the study population

In this section, the baseline characteristics of patients with HFrEF who underwent CRT-D implantation are presented. A total of 267 patients who underwent de novo CRT-D implantation were included in the study, all of whom survived at least 12 months after implantation. The procedure was performed predominantly for primary prevention (92.9%), whereas secondary prevention accounted for 7.1% of cases. Based on changes in LV EF assessed at echocardiographic follow-up performed one year after implantation, 119 patients were classified as responders, 79 as non-progressors, and 69 as progressors. No significant differences were observed among the three groups with respect to age, sex distribution, baseline NYHA functional class, or preoperative QRS duration. In the progressor population, non-LBBB QRS morphology was more frequent, and baseline LV EF was significantly higher compared with the responder group ($p = 0.02$). At the one-year follow-up after implantation, changes in LV function demonstrated marked differences among the three groups. In responders, LV EF approached or reached approximately 40%, reflecting substantial reverse remodelling, whereas in progressor patients LV EF further decreased to an average value of

approximately 22%, indicating progression of LV systolic dysfunction. When analysing post-implantation QRS duration and functional status, the most favourable results were observed among responders, while the least favourable outcomes were seen in progressor patients. Regarding comorbidities, no significant differences were observed among the three subgroups in terms of HF aetiology, prevalence of hypertension, serum creatinine and haemoglobin levels, or body mass index. However, the prevalence of diabetes mellitus was lower among responders compared with the non-progressor and progressor populations. The frequency of AF and the occurrence of prior stroke and/or TIA were significantly higher in the progressor group. Pharmacological treatment for heart failure did not differ substantially among the three cohorts, as patients received OMT according to the guidelines available during the study period. Responders remained clinically stable with lower doses of diuretics, whereas stabilisation of progressor patients required higher doses of diuretic therapy. It should be noted that at the time of the study, SGLT2 inhibitor therapy was not yet available in Hungary for the treatment of HFrEF.

4.1.2 Long-term survival according to echocardiographic response following CRT-D implantation

The classification based on echocardiographic response revealed clear prognostic differences. The mean follow-up duration was 69.7 ± 3 months in responders, 46.0 ± 3.2 months in non-progressors, and 41.9 ± 3.7 months in the progressor population, while the primary endpoint-free survival rates were 68.1%, 46.8% and 40.3%, respectively. Median survival calculated using Kaplan–Meier analysis also reflected the differences between groups: the median survival of responders was 100.2 months, compared with 70.4 months in non-progressors and 39.7 months in progressors. Log-rank analysis demonstrated significantly better survival among responder patients compared with both the non-progressor ($p = 0.002$) and progressor groups ($p < 0.0001$), while a significant difference was also observed between the non-progressor and progressor cohorts ($p = 0.03$). As this classification was based exclusively on reverse remodelling endpoints, we further analysed the role of clinical events occurring within the first year after implantation, including hospitalisation for HF and/or ICD therapy, to refine long-term outcome assessment, which is presented in the following subsection.

4.1.3 Prognostic significance of early hospitalisation for HF and ICD activity

During the first year after implantation, at least one hospitalisation due to HF and/or ICD activity occurred in 12.6% of responders, 30.4% of non-progressors and 50.7% of progressors. In the responder group, these events were predominantly isolated ventricular arrhythmias, whereas in the progressor population hospitalisation for acute HF was more frequent, either alone or in combination with ventricular arrhythmias. During the first year after implantation, inappropriate ICD activity occurred in 4.2% of responders, 5.1% of non-progressors and 4.3% of progressors, with no significant difference observed between groups. The occurrence of any HF episode or ventricular arrhythmia during the first year was associated with significantly worse long-term prognosis, irrespective of the type of event. Detailed analysis of ventricular arrhythmias demonstrated that multiple independent arrhythmic episodes requiring ATP and/or ICD shock were particularly associated with unfavourable outcomes. In contrast, arrhythmias terminated solely by ATP showed a prognosis similar to that of patients without arrhythmia events.

4.1.4 Integrated prognostic evaluation of reverse remodelling and early clinical events

Following classification of patients into responder, non-progressor and progressor groups based on reverse remodelling endpoints, we subsequently examined the prognostic impact of early clinical events occurring after CRT-D implantation. Each of these populations was further subdivided into two subgroups according to the occurrence of hospitalisation for HF and/or ICD activity within the first year after implantation, and the survival of these six subcategories was compared using Kaplan–Meier analysis. The occurrence of a clinical episode (hospitalisation for HF and/or ICD activity) within the first year was associated with significantly worse outcomes regardless of whether patients belonged to the responder, non-progressor or progressor category based on echocardiographic response. However, more detailed analysis revealed that certain subgroups demonstrated similar survival patterns. Patients classified as responders or non-progressors based on echocardiographic criteria who did not experience clinical events during the first year showed comparable survival and were therefore grouped into the “improving” cohort. In contrast, responders who experienced early clinical events had a prognosis similar to that of progressor patients without early clinical events; these subgroups together constituted the “stabilising” population. Finally, non-progressor and progressor patients who experienced clinical events within the first year exhibited similarly poor survival and were classified as the “worsening” group. Comparison of survival across the newly defined three prognostic cohorts demonstrated marked and

statistically significant differences. Median survival was 102.3 months in the improving group, 62.0 months in the stabilising population and only 24.4 months in the worsening cohort. Comparison of perioperative patient characteristics further refined these findings. Postoperative NYHA functional status differed significantly among the three newly defined cohorts. One-year LV EF after implantation, QRS duration and the magnitude of QRS shortening (Δ QRS) reached the most favourable values in the improving group, whereas no significant differences in these parameters were observed between the stabilising and worsening cohorts. The worsening population exhibited the highest prevalence of non-LBBB QRS morphology, supporting the prognostic significance of the electrical substrate. The prevalence of comorbidities was generally similar across the three groups; however, diabetes mellitus and AF were significantly more frequent in the worsening group compared with the improving cohort.

4.1.5 Predictors of favourable and unfavourable clinical outcomes

Cox regression analysis was performed to identify factors associated with long-term outcomes. Univariate analysis identified several variables that showed significant associations with prognosis. Unfavourable outcomes were associated with clinical events occurring prior to implantation or within the first year after the procedure, echocardiographic classification as a progressor, age above 75 years, chronic renal impairment, QRS shortening of less than 10 ms, and non-LBBB QRS morphology. In addition, preoperative NYHA functional class III–IV was also associated with poorer survival. In contrast, responder status determined at the one-year echocardiographic evaluation and a reduction in QRS duration exceeding 20 ms were identified as favourable prognostic indicators.

In the multivariate model, only responder status remained an independent predictor of favourable long-term clinical outcome. Conversely, independent predictors of adverse prognosis included the occurrence of clinical events before implantation or during the first year after the procedure, age above 75 years, impaired renal function, insufficient reduction in QRS duration, and non-LBBB QRS morphology.

4.2 Electromechanical and clinical effects of CSP in HFrEF with RBBB

4.2.1 Baseline demographic and clinical characteristics

Conduction system pacing was attempted in 20 consecutive patients with HFrEF and RBBB at our centre. The procedure was technically successful in 16 patients, achieving either HBP or LBBAP. In four patients, adequate lead penetration into the interventricular septum could not be achieved because of anatomical and/or technical limitations. The study population

showed a predominance of male patients. The aetiology of HF was predominantly non-ischaemic cardiomyopathy. The most common comorbidities included hypertension, diabetes mellitus, chronic renal impairment and AF.

In our patient cohort, the mean QRS duration exceeded 150 ms, while only five patients had a QRS duration between 130 and 150 ms. Typical RBBB QRS morphology was observed on the ECG in 75% of patients. In a substantial proportion of cases this was accompanied by bifascicular or trifascicular conduction disturbance, with bifascicular block present in 50% and trifascicular block in 25% of patients; however, none of the patients had high-grade AV-block requiring pacemaker implantation, and CSP was performed exclusively for resynchronisation purposes. All patients were enrolled while receiving maximally tolerated guideline-directed medical therapy for heart failure.

All patients were treated with ACE inhibitors or ARBs in 19% of cases and ARNI therapy in 81%, and all received beta-blocker therapy; MRAs were used in 93% and SGLT2 inhibitors in 63% of patients. During the six-month follow-up period, no relevant modifications were made to pharmacological or device therapy, and no additional cardiological interventions, including structural or coronary procedures, were performed.

4.2.2 Periprocedural data and electrical resynchronisation following CSP

HPB was successfully achieved in seven patients, whereas LBBAP was performed in the remaining cases, including LBBP in six patients and LVSP in three patients. The final follow-up dataset included six patients treated with HPB and ten with LBBAP, as in one patient loss of His capture shortly after the primary implantation necessitated lead repositioning, during which LVSP was achieved. When evaluating procedural complications, septal perforation occurring during transseptal lead positioning was not considered a complication, as the lead was withdrawn and repositioned according to recommended practice. Two cases of pneumothorax and one pocket haematoma requiring surgical evacuation occurred during the implantation procedures, while no other major complications were observed. CSP resulted in a significant reduction in QRS duration compared with baseline values, which may be considered an objective indicator of electrical resynchronisation.

In the case of NS-HPB, complete correction of RBBB morphology could be achieved in all patients when higher pacing outputs were applied, whereas at lower pacing amplitudes the block was only partially corrected in some cases. In contrast, S-HPB did not result in meaningful QRS normalisation, and the RBBB morphology remained identical to baseline. During LBBAP, substantial QRS shortening was observed in most patients, typically associated

with partial correction of the RBBB pattern; however, in two cases QRS duration increased. During pacing, NS-LBBP was primarily targeted rather than S-LBBP, and LVSP was used when direct conduction system capture could not be achieved. During LBBAP, a unipolar pacing configuration was initially programmed. When QRS morphology correction was insufficient, approximately 30% of patients required bipolar pacing with anodal stimulation in order to achieve further reduction of the RBBB pattern.

4.2.3 *LV reverse remodelling and echocardiographic response*

At the six-month follow-up examination, LV EF showed significant improvement compared with baseline values, increasing from $27 \pm 7\%$ to $33 \pm 9\%$ ($p = 0.01$ after BH correction), while functional parameters and dimensions of the RV did not show meaningful changes. According to the predefined echocardiographic criterion, 62.5% of patients were classified as responders, achieving an absolute increase in LV EF of approximately 10%. Improvement in LV function was accompanied by favourable changes in structural parameters, consistent with reverse remodelling. Significant reductions were observed in LV end-diastolic diameter (EDD; $p = 0.01$ after BH correction), end-systolic diameter (ESD; $p = 0.001$), end-systolic volume (ESV; $p = 0.02$) and the indexed end-systolic volume (ESVi; $p = 0.02$). In contrast, end-diastolic volume (EDV), indexed end-diastolic volume (EDVi), stroke volume (SV) and stroke volume index (SVi) did not show significant changes after BH correction.

4.2.4 *LV mechanical changes*

Detailed assessment of LV mechanical performance was performed using deformation and myocardial work parameters. At six months after the intervention, GLS demonstrated significant improvement, changing from $-7 \pm 3\%$ at baseline to $-10 \pm 4\%$ ($p = 0.004$ after BH correction), indicating favourable changes in longitudinal contractility. PSD, reflecting the degree of mechanical dyssynchrony, also decreased significantly from 126 ± 28 ms to 96 ± 23 ms (corrected $p = 0.004$), suggesting more synchronised ventricular contraction.

Myocardial work parameters further reflected improvement in mechanical performance. The GWI increased significantly from 582 ± 277 mmHg% to 840 ± 306 mmHg% (corrected $p = 0.003$), while GCW also demonstrated a substantial increase from 900 ± 374 mmHg% to 1203 ± 393 mmHg% (corrected $p = 0.006$). GWW showed a decreasing trend, although this change did not reach statistical significance. GWE improved from $71 \pm 7\%$ to $77 \pm 8\%$ (corrected $p = 0.004$), indicating improved energetic efficiency of myocardial mechanical performance.

4.2.5 *Changes in clinical parameters*

During the six-month follow-up period, no patient required hospitalisation for HF. In one case, electrical cardioversion was performed due to newly developed AF. Functional status showed favourable improvement, with the majority of patients demonstrating at least one NYHA class improvement, while functional class remained unchanged in three patients. At baseline, 87.5% of patients were classified as NYHA III and 12.5% as NYHA II, whereas at six-month follow-up the distribution changed to NYHA I: 25%, NYHA II: 50%, and NYHA III: 25% (corrected $p = 0.002$). Among laboratory parameters, NT-proBNP levels showed a significant reduction compared with preprocedural values, decreasing from 4093 ± 7215 ng/L to 2087 ± 2082 ng/L (corrected $p = 0.003$). The substantial baseline variability was influenced by one extremely high value of approximately 35,000 ng/L. Objective improvement in exercise capacity was also demonstrated by a statistically significant increase in the distance measured during the six-minute walk test, which increased by approximately 60 metres on average, from 354 ± 88 m to 411 ± 95 m (corrected $p = 0.003$).

4.2.6 *Comparative analysis of different CSP strategies*

Subgroup analysis was performed to compare periprocedural, ECG, echocardiographic and clinical parameters between patients treated with HPB and those treated with LBBAP. LBBAP demonstrated more favourable periprocedural characteristics, including shorter procedure and fluoroscopy times, lower average pacing thresholds and higher R-wave amplitudes compared with HPB. However, after applying BH correction for multiple comparisons, only the difference in pacing threshold remained statistically significant (corrected $p = 0.019$). No substantial differences were observed between the two pacing strategies with respect to clinical outcomes or echocardiographic parameters. Owing to the small number of patients in each subgroup, the statistical power of this analysis was limited, and the results should therefore be interpreted with caution. When comparing baseline and periprocedural characteristics between responders and non-responders to CSP, no variables were identified that reliably predicted therapeutic response, which is also likely attributable to the limited sample size.

5 DISCUSSION

The present thesis integrates the findings of two conceptually related investigations aimed at providing a novel perspective on the prognostic evaluation of resynchronisation therapy performed with conventional biventricular pacing and at analysing in detail the mechanical and clinical effects of CSP in patients with HFrEF.

In the first study, we evaluated the long-term prognosis and associated clinical parameters of patients who underwent implantation of a resynchronisation device with defibrillator function, and the assessment of therapeutic response was not based solely on the extent of echocardiographic reverse remodelling but also incorporated clinical events occurring within the first year after implantation. Our objective was to determine how improvement in LV function and the occurrence of early clinical events, including acute HF episodes or ventricular arrhythmias, influence long-term outcomes, and whether the combined evaluation of these factors allows more accurate prognostic stratification. Our results demonstrated that although echocardiographic response is strongly associated with long-term survival, the occurrence of early clinical events substantially modifies prognosis independently of changes in LV EF. The combined assessment of structural response to CRT and early clinical events enabled the identification of three prognostically distinct patient groups. This approach highlights that the effect of resynchronisation therapy cannot be adequately evaluated using a purely binary responder–non-responder framework, as slowing or stabilisation of disease progression may also represent a clinically meaningful therapeutic effect. Furthermore, this strategy may facilitate the early identification of patients with particularly unfavourable prognosis, in whom timely and targeted intensification of pharmacological and device-based heart failure therapy may be warranted.

In the second part of our investigation, we evaluated the effects of CSP in patients with advanced HF associated with RBBB, a population in which the effectiveness of conventional biventricular resynchronisation may be limited. Our objective was not merely to demonstrate electrical resynchronisation and reverse remodelling but to explore the complex mechanical and energetic changes induced in the LV by CSP that may underlie functional improvement and favourable clinical evolution. Although the observational nature of our study does not allow definitive causal conclusions to be drawn, our findings indicate that CSP was associated with electrical resynchronisation accompanied by improved mechanical synchrony and favourable changes in myocardial work parameters, occurring in parallel with reverse cardiac remodelling, improvement in functional status and reduction in biomarker levels.

5.1 The need for a refined definition of response to CRT – limitations of the binary approach

The traditional binary classification of response to CRT, distinguishing between responders and non-responders, is increasingly regarded as outdated. This categorisation, long used in clinical practice, does not adequately account for the progressive nature of HF or for the fact that beneficial therapeutic effects may not be reflected solely by early echocardiographic improvement. Slowing disease progression or achieving temporary clinical stabilisation may itself represent a meaningful therapeutic benefit, even when significant reverse remodelling cannot be demonstrated during the first post-implantation follow-up examinations. The classification of approximately 30–40% of patients as non-responders has contributed to an overly simplified perception that may underestimate the effectiveness of CRT and does not accurately reflect long-term prognostic differences. Recognising the limitations of the traditional binary concept of CRT response, several authors have proposed more refined approaches to prognostic stratification. Among these, the concept associated with Frank Ruschitzka and Jan Steffel places the extent of LV reverse remodelling at the centre of response definition. The original framework distinguished five prognostically distinct categories: hyper-responders, responders, non-progressors, non-responders and negative responders. In this model, hyper-responders demonstrate pronounced structural improvement with substantial reductions in LV volumes and marked increases in LV EF, while responders show more moderate but clearly measurable reverse remodelling. In non-progressors, the natural course of the disease is effectively halted and clinical status stabilises. In contrast, non-responder and progressor patients show no structural improvement in LV function and may even exhibit further deterioration accompanied by unfavourable clinical outcomes. This concept was further refined in 2025, when long-term outcome analyses led to the consolidation of the non-responder and negative responder categories into a single progressor group, while non-progression was defined as a distinct intermediate response category. This revised system distinguishes four echocardiographic response groups—super-responders, responders, non-progressors and progressors—resulting in more clearly separated prognostic populations. The echocardiographic parameters underlying this classification, primarily changes in LV EF and ESVi, represent objective and reproducible measurements that are closely associated with long-term survival and the occurrence of clinical events. Overall, the reverse remodelling-based classification represents an important step towards a more nuanced and prognostically meaningful interpretation of CRT response and provides the conceptual basis for more complex response models that integrate clinical events into the evaluation of therapeutic outcomes.

5.2 A more comprehensive interpretation of response to CRT: combining structural and clinical endpoints

In addition to the prognostic value of reverse remodelling–based classification, the need emerged to integrate structural changes with clinical status. One of the most influential approaches in this regard is the hierarchical clinical evaluation system proposed by Packer, which incorporates mortality, hospitalisation for HF and changes in functional status (NYHA class). Within this conceptual framework, Gold and colleagues analysed reverse remodelling in combination with a clinical composite endpoint in a prespecified five-year follow-up analysis of the REVERSE trial and demonstrated that the prognostic significance of structural improvement is closely associated with changes in clinical status. Patients were stratified according to the combined evolution of these two endpoints: those who showed no deterioration in either parameter had the most favourable long-term prognosis, whereas the coexistence of structural and clinical deterioration was associated with substantially worse outcomes. Patients whose condition worsened according to only one of the endpoints formed an intermediate-risk group. This combined evaluation strategy clearly demonstrated that simultaneous consideration of structural and clinical responses allows more accurate risk assessment than either component alone. Nevertheless, this model also has limitations. The clinical composite endpoint partly includes subjective elements, such as changes in NYHA functional class, which may be influenced by interobserver variability and by the patient’s subjective perception of symptoms. Another limitation is that the temporal dynamics of structural changes and clinical events may differ. Reverse remodelling often develops gradually over several months, whereas clinical deterioration or hospitalisation may occur as an acute event. The integration of these different time scales may introduce uncertainty into the categorisation, particularly when the time points of evaluation are not fully synchronised. In addition, the hierarchical weighting of the clinical composite endpoint, although clinically justified, may be statistically sensitive to a dominant component — such as mortality — potentially overriding the prognostic relevance of structural improvement.

5.3 Incorporation of objective clinical events into the evaluation of CRT response

Based on the considerations outlined above, in our study structural changes were not combined with changes in functional status but rather with objective early clinical events. Hospitalisation for HF and documented ventricular arrhythmic episodes occurring within the first year after implantation were evaluated together with the degree of reverse remodelling to establish response categories. Early clinical events occurring in any of the reverse remodelling–

defined groups — responders, non-progressors and progressors — were associated with adverse clinical outcomes and proved to be among the strongest predictors of long-term prognosis. When analysing reverse remodelling endpoints together with early clinical events, we observed prognostic overlap among certain subgroups of the original echocardiographic categories regarding long-term survival.

Responders and non-progressors without clinical events demonstrated comparable survival and were therefore grouped into a single improving cohort. In addition, responders who experienced early clinical events and progressors who remained free from events showed similar long-term outcomes and together formed the stabilised category. Finally, non-progressor and progressor patients who experienced clinical events during the first year exhibited similarly poor prognoses and were classified into the worsening group. This approach offers several advantages. First, clinical events such as hospitalisation and sustained ventricular arrhythmia represent clear, objectively documented endpoints that are less dependent on investigator judgement or the patient's subjective perception of symptoms. Second, these events carry direct prognostic significance and reflect clinical instability of the disease.

The long-term survival of the three groups defined by this method differed significantly, and the separation between survival curves proved more pronounced than when patients were classified solely according to echocardiographic reverse remodelling endpoints. The advantage of the combined approach was particularly evident among patients with the most unfavourable prognosis: identification of the worsening group was clearer than when echocardiographic progression alone was used as the defining criterion. This suggests that the evaluation of reverse remodelling alone does not always capture the high-risk state associated with clinical instability, whereas the inclusion of early objective clinical events enables more accurate identification of truly high-risk patients.

In the international context, our findings partly confirm and partly refine the conclusions of studies investigating redefined CRT response categories. In the prespecified five-year follow-up analysis of the REVERSE trial, the prognosis of patients classified as worsening was clearly less favourable than that of the improving and stabilised populations. However, differences in survival between the latter two groups were not consistently demonstrable, particularly when classification was based solely on echocardiographic parameters. A meta-analysis summarising several prospective studies using a similar conceptual approach likewise demonstrated that deterioration—whether defined by echocardiographic or clinical endpoints—has clear prognostic significance, whereas the distinction between improving and stabilised groups was not always consistent, particularly when classification relied exclusively on

structural parameters. In contrast, our model, based on the combination of structural changes and early objective clinical events, resulted in clearly distinguishable prognostic differences across all three categories. Our findings, particularly regarding the subgroup with the most unfavourable outcomes, are also consistent with observations from the ADVANCE CRT Registry. Data from this registry highlighted that clinically unstable patients who fail to show meaningful improvement after implantation have substantially worse prognoses, while therapeutic intensification in this population often remains insufficient. In that study, a considerable proportion of patients classified as non-responders (44%) did not receive additional therapeutic interventions despite higher rates of hospitalisation and mortality compared with responders. This underscores the importance of identifying truly high-risk individuals to prompt structured reassessment of treatment and, when necessary, timely therapeutic intensification.

5.4 A new direction for CRT in RBBB: CSP as physiological resynchronisation

The clinical effectiveness of CRT is closely related to baseline QRS morphology. In patients with true LBBB, the beneficial effects of biventricular pacing on mortality, hospitalisation and LV function have been clearly demonstrated in randomised trials. RBBB belongs to the non-LBBB morphology group and, when associated with HFrEF, carries a Class IIa or IIb indication for CRT in current guidelines depending on QRS duration. It is important to emphasise, however, that most large randomised CRT trials did not include a sufficiently large proportion of patients with RBBB to allow direct comparison of the effectiveness of biventricular pacing in this ECG morphology. The available evidence therefore derives mainly from subgroup analyses and meta-analyses, which suggest that in RBBB the clinical and prognostic benefit of biventricular pacing is less consistent, the therapeutic response is considerably more heterogeneous than in LBBB, and in several analyses a clear clinical advantage could not be demonstrated, with some reports even raising the possibility of unfavourable outcomes. This uncertainty has contributed to growing interest in CSP as a potential alternative to conventional biventricular pacing. Based on multicentre observational studies with relatively small sample sizes, HPB in patients with HF and RBBB morphology has been shown to achieve electrical resynchronisation by reducing QRS duration and correcting the RBBB pattern, resulting in reverse remodelling accompanied by improvement in clinical status. Technical limitations associated with HPB have led to increasing interest in LBBAP. In a multicentre observational study, Vijayaraman and colleagues performed LBBAP in 121 patients with HF and RBBB morphology, achieving an implantation success rate of 88%, and

observed improvements in LV function and clinical status comparable to those reported with HPB. However, LBBAP resulted in a smaller reduction in QRS duration and less complete correction of RBBB pattern than HPB, and the magnitude of QRS duration reduction proved to be an independent predictor of echocardiographic response in their analysis.

Considering the favourable international experience with CSP, we performed HPB or LBBAP in patients with HF and RBBB morphology who had indications for CRT. Our study was a retrospective observational analysis with a relatively small sample size (16 patients) and was not designed to directly compare CSP with conventional biventricular pacing but rather to evaluate the integrated electrophysiological, structural and functional changes induced by CSP in this specific patient population. Our results demonstrated that CSP achieved electrical resynchronisation, as reflected by a significant reduction in QRS duration and partial or complete correction of the right bundle branch block pattern. The more favourable electrical activation was followed by mechanical resynchronisation, manifested by a reduction in LV mechanical dyssynchrony. These mechanical changes were accompanied by reverse remodelling and were associated with improvements in clinical status, including functional status (NYHA class), functional capacity measured by the six-minute walk test and reductions in NT-proBNP levels. Because of the limited sample size, a direct comparison between HPB and LBBAP could only be performed to a limited extent. In terms of effectiveness, the two methods appeared broadly comparable; however, NS-HPB resulted in complete correction of RBBB morphology, whereas LBBAP generally achieved only partial attenuation. At the same time, periprocedural and electrical parameters — including lower pacing thresholds, higher sensed R-wave amplitudes and shorter procedure times — suggested certain technical advantages of LBBAP.

Our findings are broadly consistent with previous reports, as the demographic characteristics and comorbidity profile of our population did not differ substantially from those described in international cohorts. The baseline ECG characteristics of our patients frequently demonstrated complex intraventricular conduction disturbances, often in the form of bifascicular or trifascicular block, similar to the ECG patterns reported in earlier studies. The degree of electrical resynchronisation, reflected by the reduction in QRS duration, as well as the magnitude of echocardiographic improvement were also comparable to previous observations. An important difference, however, was that our cohort had a lower baseline LV EF, indicating a population with more severe systolic dysfunction. Despite this, the magnitude of improvement in LV function and clinical status was similar to that reported in earlier studies.

5.5 Mechanisms of right bundle branch block correction during CSP

Correction of the RBBB pattern, either complete or partial, is considered a marker of electrical resynchronisation and an independent predictor of favourable clinical response; however, the precise electrophysiological mechanisms underlying this phenomenon remain incompletely understood.

In our study, NS-HPB achieved voltage-dependent complete QRS correction, whereas S-HPB did not result in resolution of the right bundle branch block pattern. Similar observations have been reported in international observational studies, in which HPB applied in a comparable patient population resulted in attenuation of RBBB in a substantial proportion of cases, predominantly during NS-HPB, while correction was less frequent during S-HPB. In a study conducted in a population with preserved LV function, NS-HPB attenuated the RBBB pattern in a voltage-dependent manner, whereas S-HPB failed to correct the conduction abnormality. Considering the frequent presence of complex conduction disturbances, these observations suggest that the site of conduction block may often be located distal to the His bundle. Non-selective stimulation at higher pacing outputs may directly correct RBBB that is at least partly functional in nature, but alternative conduction pathways may also be recruited, leading to earlier activation of the myocardium distal to the block. Even without direct restoration of conduction through the right bundle branch, a “fusion” pattern of ventricular activation may develop through the combination of conduction via the His bundle, still displaying a RBBB pattern, and myocardial pacing of the RV septum.

During LBBAP, attenuation of the RBBB pattern is typically observed during NS-LBBP or LVSP. The combined activation of the left bundle branch conduction system and the RV septal myocardium may reduce RV activation delay and thereby improve the temporal synchrony of interventricular activation while preserving synchronous LV contraction. In contrast, during S-LBBAP the RV septal myocardium is not directly activated, and therefore the full RBBB pattern and the associated interventricular dyssynchrony may persist. When LBBAP did not result in attenuation of the RBBB pattern, further reduction in QRS duration could in some cases be achieved through bipolar pacing with anodal capture at the ring electrode, which produced simultaneous activation of the RV septum. This phenomenon was observed in approximately one third of our patient cohort and has also been reported with similar frequency in international studies as a mechanism for additional QRS correction. In a substantial proportion of our patients, RBBB was accompanied by first-degree AV-block, in which case targeted optimisation of atrioventricular delay may restore AV synchrony and contribute to improvement in clinical status.

Overall, correction of RBBB during CSP is not solely the result of direct stimulation of the conduction system but rather reflects a complex interaction between activation of the specialised conduction system and septal myocardial stimulation, which reduces interventricular delay and leads to electrical and subsequently mechanical improvement in parallel with restoration of AV synchrony.

5.6 Mechanical consequences of electrical resynchronisation

The reduction in QRS duration and correction of RBBB pattern indicating electrical resynchronisation were accompanied by favourable changes at the mechanical level. The decrease in PSD indicated a more homogeneous timing of LV contraction, demonstrating that restoration of electrical activation was associated with mechanical resynchronisation. According to previously published studies, reductions in PSD are closely related to improvement in LV function, the development of reverse remodelling and favourable clinical outcomes. Restoration of mechanical synchrony was also accompanied by improvement in myocardial work parameters, whose prognostic relevance has been emphasised in several earlier investigations. In addition, improvements in myocardial work parameters have been associated with favourable changes in myocardial energetic efficiency. In our study, CSP was followed by significant increases in global myocardial work index, constructive work and mechanical efficiency, suggesting that improved mechanical synchronisation was associated with more efficient LV mechanical performance and may represent a potential link between reverse remodelling and clinical improvement. At the same time, it should be emphasised that in the absence of a control group — whether treated with optimal medical therapy alone or with conventional biventricular pacing — causal conclusions cannot be drawn from the observed mechanical changes, and confirmation of these findings will require prospective randomised studies.

5.7 Limitations

Both studies were based on retrospective data collection related to CRT, which carries the inherent risk of selection bias and the influence of uncontrolled confounding factors. The single-centre design represents a significant limitation for the interpretation and generalizability of the results, as the patient population, implantation practices, and follow-up protocols of a given institution may differ from those of other centres. The observational nature of the studies, without the inclusion of a control group, substantially limits the ability to establish causal relationships. The relatively small sample size, particularly in the CSP study ($n = 16$), represents

an additional limitation. The limited number of cases reduces statistical power, increases the probability of type II error, and does not allow for reliable subgroup analyses. Furthermore, the heterogeneous intervention strategy, involving both HBP and LBBAP, may have introduced additional variability into the results, which could potentially be mitigated in a larger study population. In the analysis evaluating the prognosis of conventional CRT therapy, only patients who survived at least 12 months after device implantation were included. This may have introduced survival bias, as patients with the poorest prognosis who experienced early mortality were not represented in the analysis. Finally, the follow-up period in the CSP study was limited to 6 months, allowing primarily the evaluation of short-term changes in structural and functional parameters. Long-term clinical outcomes - such as mortality, hospitalization due to heart failure, and arrhythmic events - were not assessed in this cohort; therefore, the prognostic significance of the observed mechanical improvements cannot be directly established.

6 SUMMARY AND CLINICAL SIGNIFICANCE OF OUR FINDINGS

The results of our work contribute to a more contemporary and integrated interpretation of resynchronisation therapies applied in HF. We demonstrated that the response to CRT cannot be evaluated solely based on volumetric reverse remodelling, but that the combined consideration of structural changes and early clinical events is necessary to determine the true prognostic risk. The occurrence of an early major clinical episode proved to be a strong negative prognostic marker independent of echocardiographic improvement, highlighting the need to reconsider current strategies for patient follow-up and risk stratification.

Our findings confirm that the effect of CRT should be interpreted as a disease-modifying process that may lead to different phenotypes through reverse remodelling, slowing of disease progression or prevention of clinical deterioration. The structural-clinical composite approach proposed in our study enables more precise prognostic stratification and may support personalised follow-up strategies, while also allowing the identification of patient groups with particularly unfavourable prognosis who require intensified monitoring and optimisation of therapy.

Our findings regarding conduction system pacing are particularly relevant in patients with RBBB morphology, in whom the effectiveness of conventional biventricular CRT may be limited. We demonstrated that CSP not only produces electrical correction but also favourably influences mechanical dyssynchrony, deformation parameters and myocardial work efficiency. These findings provide a pathophysiological rationale for the use of a more physiological

activation strategy in a patient population in which therapeutic response has traditionally been heterogeneous.

Overall, our work shifts the evaluation of resynchronisation therapy from a purely volume-based perspective towards a complex integration of electromechanical and clinical parameters, thereby supporting more accurate prognostic assessment and more personalised therapeutic decision-making.

7 NOVEL SCIENTIFIC FINDINGS

In this thesis we investigated the clinical and structural effects of resynchronisation strategies applied in HF_{rEF}. We developed a new evaluation framework for the response to conventional CRT that integrates structural and clinical parameters, and we analysed the electromechanical effects of CSP, including HPB and LBBAP, in patients with RBBB morphology. Our findings contribute to a more contemporary prognostic interpretation of CRT response and to a deeper understanding of the mechanical effects of CSP in a population in which the effectiveness of conventional biventricular pacing is limited.

- We demonstrated that, based on echocardiographic reverse remodelling endpoints (LV EF), the population undergoing CRT-D implantation can be categorised into responder, non-progressor and progressor phenotypes. Survival differed markedly and significantly among the three groups, with the progressor group showing the least favourable prognosis, whereas responders demonstrating reverse remodelling had the best long-term outcomes. Our findings confirm that the traditional responder–non-responder dichotomy is insufficient from a prognostic perspective.
- We showed that the occurrence of a major clinical episode within the first year after implantation (hospitalisation for HF and/or malignant ventricular arrhythmia) is associated with significantly worse survival independently of the extent of echocardiographic reverse remodelling.
- By combining the occurrence of a major clinical event within one year with reverse remodelling endpoints, we introduced a new prognostically differentiated classification replacing the conventional three-category system (responder–non-progressor–progressor). Based on this composite endpoint, patients were categorised into improving, stabilised and worsened groups. Our results support the concept that the effect of CRT should be interpreted as a disease-modifying therapy and that therapeutic response cannot be reduced solely to volumetric parameters.

- We demonstrated that CSP, including both HPB and LBBAP techniques, results in electrical resynchronisation with significant QRS shortening and structural remodelling (improvement in LV EF and reduction in ventricular volumes) in patients with HF and RBBB QRS morphology, accompanied by improvement in clinical status.
- In patients with typical RBBB morphology, we analysed for the first time the mechanical consequences of CSP using deformation echocardiography (GLS) and myocardial work parameters. We demonstrated that CSP reduces LV mechanical dyssynchrony and improves GLS, accompanied by favourable changes in myocardial work and mechanical efficiency.

8 OWN PUBLICATIONS



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List of publications related to the dissertation

1. **Tóth, A. Z.**, Nagy, L., Jenei, C., Ráduly, A. P., Sándorfi, G., Szabó, K. M., Kiss, A., Nagy, L. T., Szilágyi, G. I., Csanádi, Z.: Conduction System Pacing Improved Cardiac Functions, Myocardial Work and Functional Capacity in Heart Failure with Reduced Ejection Fraction and Right Bundle Branch Block.
J Clin Med. 15 (1), 1-14, 2026.
DOI: <http://dx.doi.org/10.3390/jcm15010232>
IF: 2.9 (2024)
2. **Tóth, A. Z.**, Nagy, L., Szabó, K. M., Rácz, V., Kiss, A., Sándorfi, G., Borbély, A., Nagy, T. L., Csanádi, Z.: Early occurrence of heart failure hospitalization or ventricular arrhythmia re-define the long-term prognosis after CRT.
ESC Heart Failure. 12 (4), 2780-2790, 2025.
DOI: <http://dx.doi.org/10.1002/ehf2.15274>
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List of other publications

3. Szabó, K. M., **Tóth, A. Z.**, Nagy, L., Nagy, L. T., Sándorfi, G., Clemens, M., Nagy, A. C., Ráduly, A. P., Borbély, A., Barta, J., Csanádi, Z.: Comparable Benefits in Heart Failure Hospitalization and Survival with Sacubitril/Valsartan Therapy in CRT Nonresponders and HFrEF Patients Without CRT Indication.
J Clin Med. 14, 1-12, 2025.
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4. Szabó, K. M., **Tóth, A. Z.**, Nagy, L., Rácz, V., Pólik, Z., Hódosi, K., Nagy, A. C., Barta, J., Borbély, A., Csanádi, Z.: Add-on Sacubitril/Valsartan Therapy Induces Left Ventricular Remodeling in Non-responders to Cardiac Resynchronization Therapy to a Similar Extent as in Heart Failure Patients Without Resynchronization.
Cardiol Ther. 13 (1), 149-161, 2024.
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IF: 2.7
5. Szabó, K. M., **Tóth, A. Z.**, Borbély, A., Csanádi, Z., Nagy, L.: A kardiális reszinkronizációs kezelésre adott válasz újraértelmezése és a terápiás hatékonyság javításának lehetősége.
Cardiol. Hung. 54 (3), 227-233, 2024.
DOI: <http://dx.doi.org/10.26430/CHUNGARICA.2024.54.3.227>
6. Nagy, L., **Tóth, A. Z.**, Kiss, A., Szabó, K. M., Nagy, L. T., Csanádi, Z., Sándorfi, G.: Pacemakerkezelés fiziológiás ingerületvezetőrendszer-ingerléssel: múlt, jelen és jövő.
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DOI: <http://dx.doi.org/10.26430/CHUNGARICA.2023.53.3.225>
7. **Tóth, A. Z.**, Csanádi, Z., Sándorfi, G., Nagy, L.: A kardiális kontraktilitás modulációjával elért bal kamrai reverz remodelling egy dilatatív cardiomyopathiás betegben.
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10 APPENDIX

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