Insights into left ventricular dyssynchrony: Consequences for myocardial function and response to cardiac resynchronization therapy

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2. LIST OF PAPERS

1. Afterload Hypersensitivity in Patients With Left Bundle Branch Block.
Aalen J, Storsten P, Remme EW, Sirnes PA, Gjesdal O, Larsen CK, Kongsgaard E, Boe E, Skulstad H, Hisdal J, Smiseth OA.
JACC Cardiovasc Imaging 2019;12(6):967-977.

2. Mechanism of Abnormal Septal Motion in Left Bundle Branch Block: Role of Left Ventricular Wall Interactions and Myocardial Scar.
Aalen JM, Remme EW, Larsen CK, Andersen OS, Krogh M, Duchenne J, Hopp E, Ross S, Beela AS, Kongsgaard E, Bergsland J, Odland HH, Skulstad H, Opdahl A, Voigt JU, Smiseth OA.
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3. Imaging predictors of response to cardiac resynchronization therapy: Left ventricular work asymmetry by echocardiography and septal viability by cardiac magnetic resonance.
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3. ABBREVIATIONS

ACE = angiotensin-converting enzyme

ARB = angiotensin receptor blocker

ARNI = angiotensin receptor-neprilysin inhibitor

AUC = area under the curve

AV = atrioventricular

CI = confidence interval

CMR = cardiac magnetic resonance imaging

CRT = cardiac resynchronization therapy

CRT-D = cardiac resynchronization therapy defibrillator

CRT-P = cardiac resynchronization therapy pacemaker

CX = circumflex coronary artery

dP/dt_{min} = peak rate of pressure decay

ECG = electrocardiogram

EF = ejection fraction

ESC = European Society of Cardiology

FDG-PET = ^{18}F-fluorodeoxyglucose positron emission tomography

GLS = global longitudinal strain

HF = heart failure

HFrEF = heart failure with reduced ejection fraction (<40%)

HFmrEF = heart failure with mid-range ejection fraction (40-49%)

HFpEF = heart failure with preserved ejection fraction (≥50%)

ICC = intra-class correlation coefficient

ICD = implantable cardioverter-defibrillator

IM-EMG = intramyocardial electromyogram

LA = left atrial

LAD = left anterior descending coronary artery

LBBB = left bundle branch block

LGE = late gadolinium enhancement

LV = left ventricular

LVP = left ventricular pressure

LW-S = lateral wall-to-septal

NYHA = New York Heart Association

RBBB = right bundle branch block

ROC = receiver operating characteristic

RV = right ventricular

SGLT2 = sodium-glucose cotransporter 2

SPWMD = septal-to-posterior wall motion delay

TAVR = transcatheter aortic valve replacement

2D = two-dimensional

4. INTRODUCTION

Dyssynchrony

The normal left ventricle is characterized by synchronous contractions in all segments, ensuring effective pumping of blood with minimal waste of myocardial energy. A synchronous contraction pattern depends on both rapid electrical activation through a specialized conduction system and normal myocardial contractile function. If regional timing of contractions are out of phase, the term dyssynchrony is used (1).

Normally, left ventricular (LV) electrical activation starts when an electrical impulse enters the ventricle through the atrioventricular (AV) node. The impulse soon reaches the Bundle of His, which divides into the right and left bundle branches. The bundle branches continue along the interventricular septum towards the apex before the right bundle branch turns towards the right ventricular (RV) free wall, and the left bundle branch towards the LV free wall. Furthermore, the conduction system is divided into an extensive network of Purkinje fibers ensuring complete coverage of both ventricles. In some patients, however, there is a block in the system and the consequence is slow electrical activation through normal myocardial tissue so that areas distal to the block become late-activated with delayed contraction. This phenomenon is known as electromechanical dyssynchrony. Specifically, if the block occurs in the left bundle branch, it is named left bundle branch block (LBBB) and causes dyssynchronous LV contractions with clinically important hemodynamic effects on LV function (2). Similarly, a block in the right bundle branch causes right bundle branch block (RBBB) with effects on RV contraction pattern, but is less frequently of clinical importance.

Dyssynchrony also occurs without electrical activation delay as with primary mechanical dyssynchrony due to regional myocardial ischemia or regional loading abnormalities, and with abnormalities in excitation-contraction coupling (1, 3). Moreover, dyssynchrony occurs at different anatomical levels. AV dyssynchrony is caused by a block in the AV node and may have negative impact on LV filling due to premature atrial contraction. Interventricular dyssynchrony is due to different timing of contraction in the right and left ventricle, whereas the term intraventricular dyssynchrony is used when dyssynchrony occurs within the ventricle. As LV intraventricular dyssynchrony has been considered the main target to understand why patients respond to cardiac resynchronization therapy (CRT) (4), the main focus for this synopsis will be LV intraventricular dyssynchrony in the setting of LBBB.

Left bundle branch block

In clinical practice, the diagnosis of LBBB is based on the electrocardiogram (ECG). According to the European Society of Cardiology (ESC), main criteria include a wide QRS complex (≥120

ms), QS or rS in lead V1, broad R waves in leads I, aVL,V5 or V6 and absent Q waves in V5 and V6 (5). These criteria, however, are based on dog studies from the 1940s and more recent work using endocardial mapping have demonstrated that more than 30% of patients fulfilling such criteria do not have complete LBBB with delay between electrical activation of RV and LV endocardium (6). As illustrated in Figure 1, for the individual patient, there is typically a sudden increase in QRS duration with onset of LBBB. Some patients, however, develop wide QRS over years due to hypertrophy or other pathologies. These patients may fulfil classical criteria for LBBB, but often they have a wide QRS without criteria for LBBB or RBBB which is termed nonspecific intraventricular conduction disturbance (7). There has been several attempts to improve ECG criteria for LBBB. Alternative definitions of a "true" LBBB are generally stricter than the ESC criteria. A well-known example is the criteria proposed by Strauss et al. where QRS duration should be at least 130 ms for women and at least 140 ms for men together with mid-QRS notching in at least two lateral leads (8). A wide QRS with typical LBBB activation pattern may also be seen during RV pacing, especially if the lead is placed in the RV free wall, and may have similar consequences for LV function as LBBB (9).

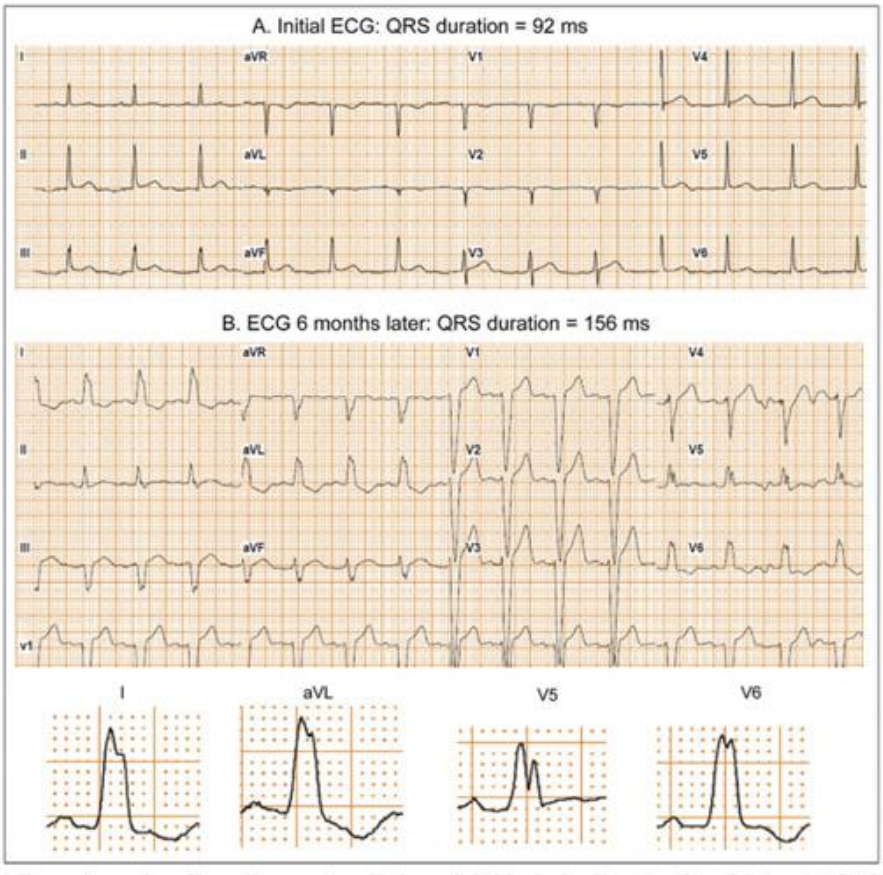

Figure 1. Two electrocardiogram (ECG) recordings from a 75 year old patient who develops left bundle branch block with sudden QRS widening. There is typical mid-QRS notching in leads I, aVL, V5 and V6. Modified from Strauss et al. with permission (8).

The prevalence of LBBB is highly age-dependent with increasing prevalence in older age. During middle age, different studies have found a prevalence of about 0.5 %, higher in men than women (10, 11). LBBB is frequently associated with other cardiac diseases such as coronary artery disease, hypertension and cardiomyopathies, but may also be present in presumably healthy patients without other signs of heart disease. In some cases, the block is caused by acute ischemia, post-infarct scar or transcatheter aortic valve replacement (TAVR), but the precise mechanism is often unknown.

LBBB is associated with increased cardiovascular mortality in all age groups (12) and in patients without known heart disease (13). Still, it has been debated whether LBBB itself causes cardiovascular disease or if it is an innocent bystander. Previously, heart failure (HF) in LBBB was mostly thought to be a result of coexisting subclinical myocardial disease (11, 14). During the last years, however, several studies have argued in favor of LBBB as an independent contributor to heart failure with reduced ejection fraction (HFrEF) both in patients with and without pre-existing HF (15-20). This hypothesis is supported by experimental studies and the large body of evidence for LV reverse remodeling and improved survival in patients undergoing CRT, which to a large extent corrects the conduction delay. In contrast to patients with LBBB and HFrEF, there is no consensus on how to manage patients with LBBB and preserved LV ejection fraction (EF). A retrospective study of 100 patients with LBBB and normal LVEF found that 36% developed LVEF <45% over a period of 4 years (21). This means that most patients maintained systolic function within normal limits, but a substantial number showed LV remodeling and the authors were not able to identify risk factors. Interestingly, however, in the Losartan Intervention For Endpoint Reduction (LIFE) study, the authors found that hypertensive LBBB patients were almost twice as likely to be hospitalized for HF as hypertensive control patients (22), possibly suggesting hypertension as a particularly important risk factor in LBBB patients. Therefore, there is need to improve understanding on how LBBB causes HF and, specifically, to explore the interaction between blood pressure and LV dyssynchrony.

In experimental studies, induction of LBBB leads to dyssynchrony with inefficient LV contractions and immediate reduction in LV systolic function (23, 24) (Figure 2). In patients, LBBB has been associated with reduced LV systolic function even in individuals where LVEF is within normal limits (25, 26). The early activation of the septum leads to an early and unopposed septal contraction immediately before and during isovolumic contraction when LV pressure (LVP) is low (preejection shortening) (Figure 2 and 3C). Hence, blood is displaced towards the LV lateral wall, which is still relaxed and therefore stretched. This leads to increased preload on the LV lateral wall with subsequent powerful contraction according to the Starling mechanism (27-29). Blood is pushed back towards the septum, which is often stretched (rebound stretch) thereby absorbing energy from work performed by the LV lateral wall (30). The result is slowing of LVP rise and prolongation of the isovolumic

contraction phase (Figure 2). During mid ejection there is usually shortening in both walls, followed by premature termination of septal shortening with late-systolic septal stretch. The result is substantial reduction in septal systolic shortening (Figure 2 and 3C). In the late-activated LV lateral wall, on the other hand, there is delayed termination of contraction with post-systolic shortening.

In addition to its effect on LV systolic function, the dyssynchronous contraction pattern of LBBB has negative effects on parameters of LV diastolic function (26) and it may both cause and aggravate mitral regurgitation (31, 32). The latter is supported by the observation that CRT reduces moderate or severe mitral regurgitation to non-significant levels in about one third of LBBB patients (33) (Figure 3E).

The dyssynchronous contraction pattern in LBBB was first visualized by M-mode echocardiography almost fifty years ago (34, 35). With the introduction of CRT in the early 2000s, numerous timing-based echocardiographic indices were developed to assess LV dyssynchrony and improve patient selection for CRT. One example is the Yu index which is calculated as the standard deviation of time to peak systolic contraction of 12 LV segments (36), another is the septal-to-posterior wall motion delay (SPWMD) which is measured by M-mode in the parasternal long-axis view (37). The most typical visual features of LBBB during echocardiography, however, is abnormal septal motion and transverse motion of the apex. Commonly these motions are referred to as septal flash (38) and apical rocking (39). As illustrated in Figure 3C, septal flash can be defined as the rapid left- and rightward motion of the interventricular septum during early systole. Apical rocking, on the other hand, is a right- and leftward motion of the apex, which is pulled back and forth by contractions in the septum and LV lateral wall (Figure 3D). In the last decades, strain echocardiography has emerged as a clinically available tool and has allowed new ways to assess LV dyssynchrony (40-43).

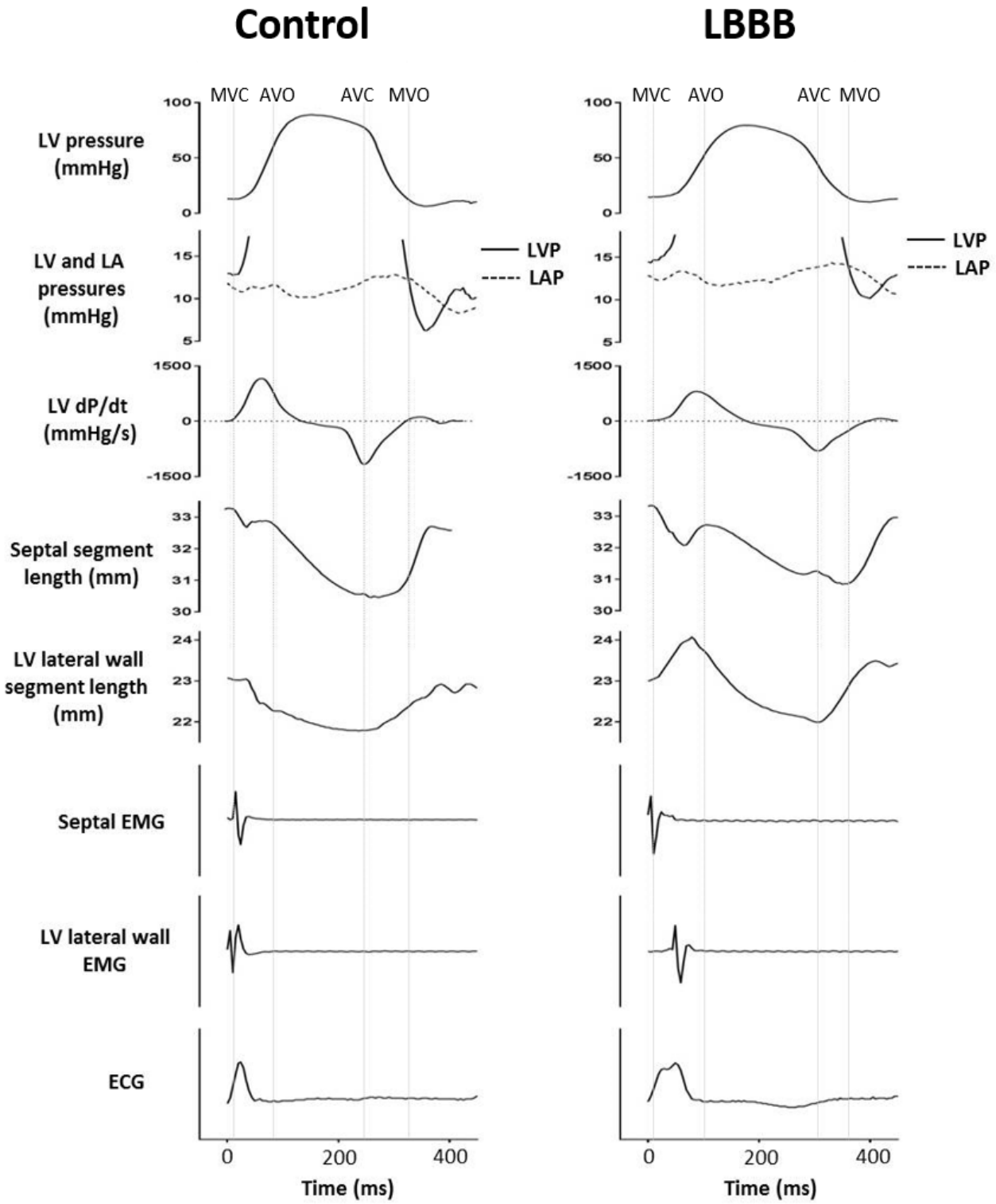

Figure 2. Hemodynamic parameters from a representative animal during control conditions (left panel) and after induction of left bundle branch block (LBBB) (right panel). LBBB causes a dyssynchronous contraction pattern with prolonged isovolumic contraction phase and reduced LV dP/dtmax (peak rate of left ventricular pressure rise). AVO = aortic valve opening, AVC = aortic valve closure, ECG = electrocardiogram, EMG = electromyogram, LA = left atrial, LAP = left atrial pressure, LV = left ventricular, LVP = left ventricular pressure, MVO = mitral valve opening, MVC = mitral valve closure.

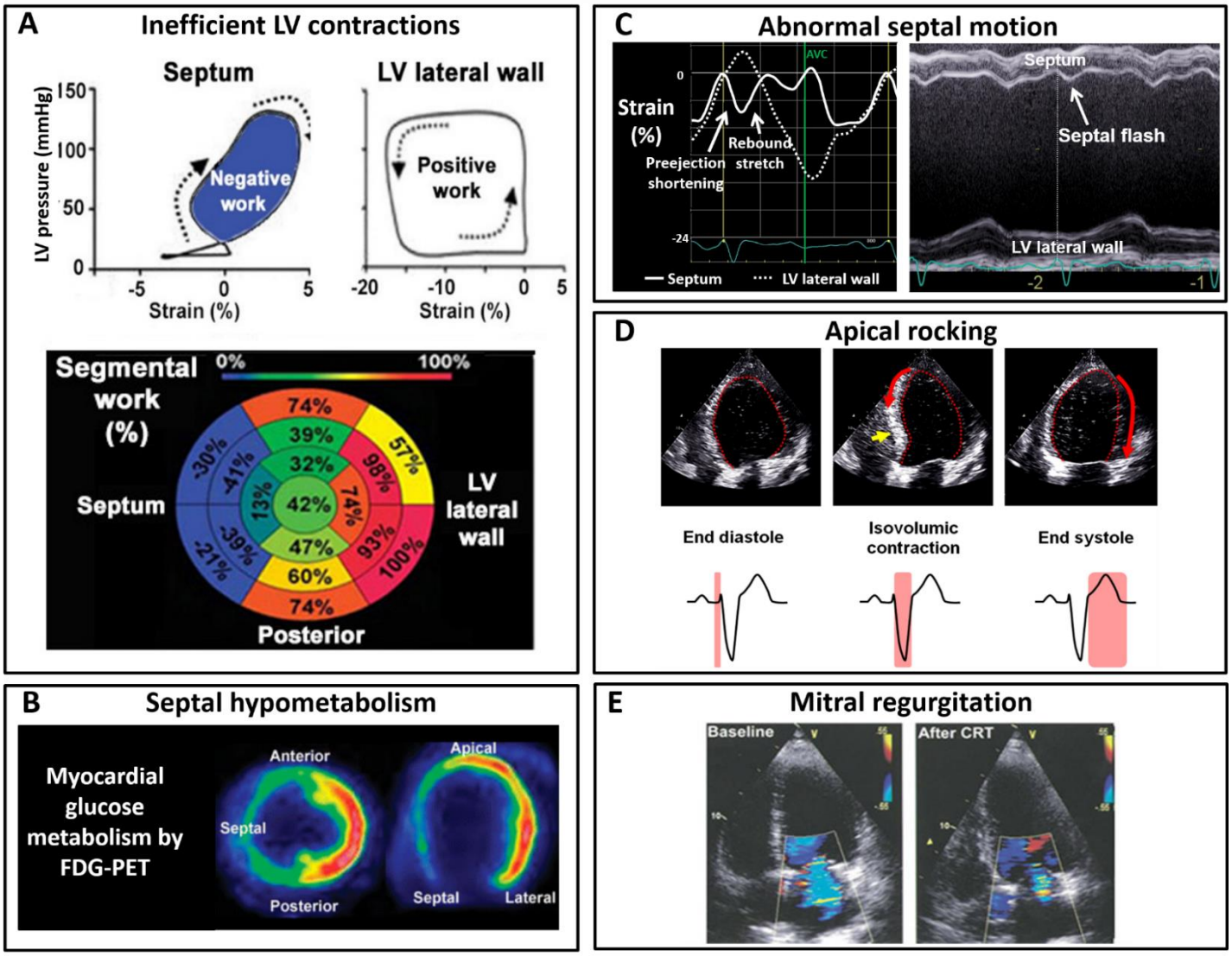

Figure 3. Left ventricular (LV) mechanical and metabolic features of left bundle branch block (LBBB). In LBBB there are typically inefficient LV contractions due to abnormal septal motion with reduced septal shortening, work and metabolism. Reproduced with permission (2).

Afterload

Afterload represents the load on the ventricle during contraction, as opposed to preload which is the load prior to contraction. A direct measure of afterload is ventricular wall stress which represents the load imposed on the myocardial fibers. According to the law of Laplace, wall stress is determined by (transmural) ventricular pressure, wall thickness and radius of curvature. Afterload increases with increased ventricular pressure, a thinner wall and larger radius (44). Moreover, afterload depends on extracardiac factors such as peripheral arterial resistance, arterial compliance and inertia, which are commonly described using a Windkessel model (45). In clinical practice, LVP or systolic blood pressure (in the

absence of significant LV outflow obstruction) is often used as a simplified measurement of LV afterload and may serve as a reasonable simplification, especially when assessments are performed within the same patient. In ventricles with regional geometrical differences like asymmetric hypertrophy, afterload may vary between different segments. Furthermore, afterload dynamically varies during systole as pressure and geometry change. These factors are of special importance in LBBB where time of contraction differs between different segments and dyssynchronous deformations result in asymmetric geometry, resulting in heterogeneous afterload. In the present thesis, we study both the effect of afterload on regional LV function and the effect of increased afterload on global LV function.

Myocardial work

As shown by Suga in the late 1970s, the area of the LV pressure-volume loop reflects stroke work (external myocardial work) and myocardial oxygen consumption (46). Similarly, it was later shown that the area of the force-segment length loop reflected segmental myocardial work and oxygen consumption (47, 48). In clinical practice, however, it is difficult to calculate force (which is similar to wall stress) due to the need for continuous recordings of radius of curvature and wall thickness in addition to pressure. Instead, it has been shown that substituting force with pressure provides a reasonable estimate of segmental work during most circumstances (49). Furthermore, segment length can be replaced by strain as dimension measurement with the limitation that it only provides a relative length. Still, the need for invasive measurement of LVP has limited the use of pressure-dimension loops in patients. Recently, however, the innovation of a non-invasive LVP curve based on brachial systolic cuff pressure and valvular event timing has enabled non-invasive estimation of myocardial work (50). Pressure-strain loops based on non-invasive LVP and strain by speckle-tracking echocardiography have been shown to correlate well with both invasive pressure-segment length loops in animals and with regional metabolism given by ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) in LBBB patients (50-52). The method has recently been incorporated in commercial software (GE Echopac 202, Horten, Norway) and is now widely available. Recently, normal values for global work parameters were published (53).

A significant limitation with strain alone as parameter of systolic function, is the lack of information on afterload. During LBBB, loading conditions in the septum are abnormal with a substantial amount of shortening performed during low LVP and, therefore, integration of afterload is of special importance (9). Myocardial work takes this aspect of dyssynchrony into account. Additionally, myocardial work takes into account both positive and negative work. Per definition, work performed during segmental shortening is positive (i.e. counterclockwise rotation of the pressure-strain loop) and work during segmental

lengthening (stretch) is negative (i.e. clockwise rotation of the pressure-strain loop). During LBBB, both early-systolic septal rebound stretch and late-systolic septal stretch represent negative work and in some cases there is even net negative septal work (as illustrated in Figure 3A). This means that contribution from the septum, which makes up approximately one third of LV mass, to LV systolic function is lost and instead the septum absorbs energy generated in the LV free wall (30). Reduced septal work explains the finding of reduced septal metabolism and perfusion, which is typical in LBBB patients despite normal coronary anatomy (Figure 3B) (50, 54, 55). Furthermore, the increased workload on the LV free wall is a stimulus to adverse remodeling (2, 29, 56). Hence, during LBBB there is typically marked work asymmetry between the septum and LV lateral wall leading to thinning of the septum and concentric hypertrophy of the LV lateral wall (57, 58).

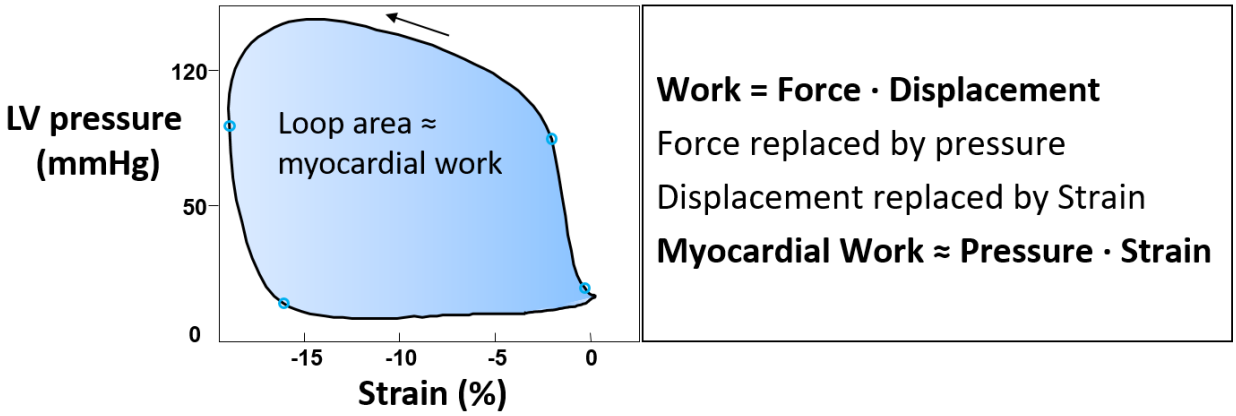

Figure 4. Concept of the myocardial work index. Arrow indicates counterclockwise rotation during systole, which means systolic shortening and positive work. Blue circles represent valvular events. LV = left ventricular.

Heart failure

HF is defined as a clinical syndrome characterized by typical symptoms caused by a structural or functional cardiac abnormality resulting in reduced cardiac output or elevated intracardiac pressures at rest or during exercise (59). It constitutes a major and growing medical problem worldwide as well as a major economic burden on health care systems (60). Diagnosis is typically made based on history, physical examination, ECG, pro-BNP, chest x-ray and echocardiography. HF can be acute or chronic; often acute HF presents in patients with large myocardial infarctions or pre-existing chronic HF. In the following, we will focus on chronic HF. The two main types of HF are HFrEF (LVEF <40%) and heart failure with preserved ejection fraction (HFpEF) (LVEF ≥50%). In the ESC guidelines there is also a third category named heart failure with mid-range ejection fraction (HFmrEF) with LVEF 40-49% (59). Both patients with HFrEF and HFpEF show high rates of five years mortality, in particular patients who have been hospitalized due to decompensation (61). There are,

however, several important differences between the two types regarding etiology and treatment. In the following, we will focus on HFrEF since this it is most important in the setting of LBBB and CRT.

First, it is important to establish underlying etiology and treat accordingly whenever possible. For example, in patients with HF partly or completely due to coronary artery disease, it is important to ensure proper revascularization. Similarly, it is essential to establish rate control in patients with tachycardiomyopathy.

There are several well-documented pharmacological treatments for HFrEF which are indicated independent of underlying etiology. Angiotensin converting enzyme (ACE) inhibitors and beta blockers are proven to reduce morbidity and mortality, and should be gradually up-titrated to target doses in all patients (59). Furthermore, in patients with LVEF ≤35% that are still symptomatic, an aldosterone receptor antagonist should be added. For patients that are intolerable to ACE inhibitors, an angiotensin receptor blocker (ARB) is an adequate substitute. A few years ago, a new drug combining an ARB with a neprilysin inhibitor (angiotensin receptor-neprilysin inhibitor (ARNI)) was shown to reduce mortality and HF hospitalizations as compared to standard treatment with an ACE inhibitor in symptomatic HFrEF patients (62). The span of indications for ARNI are currently increasing. More recently, it was found that the antidiabetic sodium-glucose cotransporter 2 (SGLT2) inhibitor dapagliflozin reduces risk of worsening HF and death among HFrEF patients with and without diabetes (63). Furthermore, there were similar findings for empagliflozin indicating a SGLT2 class effect on HFrEF (64). Thus, it is likely that SGLT2 inhibitors will play an important role in the future treatment of HFrEF although they are not yet included in guidelines. In addition to the abovementioned agents, diuretics are commonly used to relieve symptoms, but their effect on mortality remains uncertain.

Treatment in HFrEF is not limited to medical therapies. Implantable cardioverter-defibrillator (ICD) and CRT are important device therapies in selected patients. Moreover, some patients with end-stage HF are candidates for left ventricular assist device or heart transplantation. The main indications for ICD are either previous history with ventricular arrhythmia (secondary prevention) or patients with LVEF ≤35% due to ischemic or dilated cardiomyopathy (primary prevention). In addition, there are specific recommendations for ICD in hypertrophic cardiomyopathy, arrhythmogenic cardiomyopathy and inherited arrhythmia syndromes. It is important to emphasize that the ICD does not interfere with the course of HF itself, but prevents sudden cardiac death from arrhythmias. Hence, largest benefit is seen in patients with high risk of arrhythmias (typically in patients with secondary prevention).

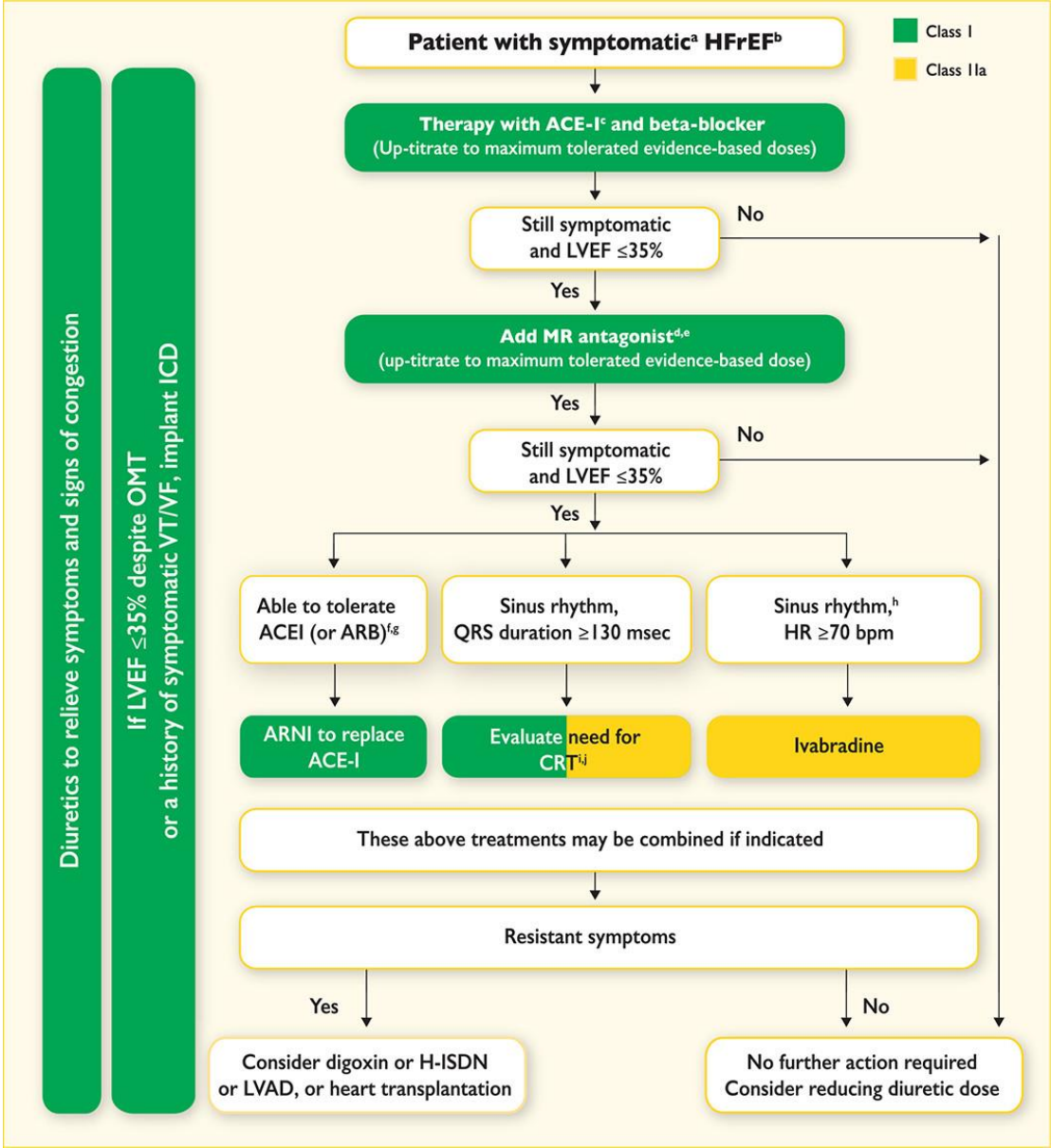

Figure 5. Treatment algorithm for heart failure with reduced ejection fraction (HFrEF) (ESC guidelines 2016). Reproduced with permission (59).

Cardiac resynchronization therapy

LBBB is present in as many as 25% of HF patients and is associated with increased mortality as compared to HF patients with narrow QRS (65). In the last 20 years, CRT has emerged as an essential part of HF therapy in such patients. At group level, CRT has major positive effects on functional outcomes, morbidity and mortality (66, 67). The main concept of CRT is to resynchronize LV contractions. This is achieved through biventricular pacing, which ensures synchronized activation of both ventricles. This being said, there is no clear evidence

that biventricular pacing is superior to LV only pacing (5). Moreover, the effect of CRT is not limited to LV dyssynchrony and other effects such as AV resynchronization, reduction of mitral regurgitation and prevention of symptomatic bradycardia, may play an important role (59, 68, 69). As with conventional 2-chamber pacemakers, CRT usually consists of one lead in the right atrium and one in the right ventricle. Additionally, in CRT, there is a third lead most often placed in the posterolateral wall of the left ventricle. The LV lead is often positioned in a coronary vein, which is reached through the coronary sinus. In some patients, however, the lead is surgically attached to the epicardium, usually via thoracotomy. CRT may be implanted as a solely biventricular pacemaker (CRT-P) or combined with an ICD (CRT-D).

The current ESC indication for CRT is HFrEF with LBBB (QRS duration ≥130 ms) or non-LBBB (QRS duration ≥150 ms), HF symptoms (New York Heart Association (NYHA) class II-IV) and LVEF ≤35% (59). Criteria are somewhat stricter and recommendation weaker for patients with atrial fibrillation as there is less evidence. Before CRT is considered, all patients should be optimally revascularized and receive optimal medical HF therapy as indicated in Figure 5. There is also indication for upgrade to CRT among patients with conventional pacemakers or ICD when there is a high percentage of ventricular pacing and declining LV systolic function. Furthermore, in patients in need of a conventional pacemaker with reduced LVEF where a high percentage of ventricular pacing is expected, direct implantation of CRT is preferred. The choice of CRT-P or CRT-D depends on the presence and strength of ICD indication and whether the main purpose of treatment is symptom relief or life prolongation. It is noteworthy that while price and complication rates are considerably higher, the mortality benefit of CRT-D over CRT-P is rather uncertain in non-ischemic patients (70).

In contrast to most other pacemaker therapies, it is important to ensure the highest possible amount of pacing with CRT. Percentage biventricular pacing should ideally be >99% and medical therapy to reduce the number of extrasystolic beats or to prevent tachyarrhythmia may be indicated. In particular, patients with atrial fibrillation is a challenging group where AV node ablation is often needed to ensure adequate percentage pacing (5).

Considering LBBB as a potential underlying cause of HF, it may seem paradoxical that medical treatment should be tried before treating LBBB with CRT. In fact, a recent study showed that HFrEF patients with LBBB seem to have less effect of medical heart failure therapy compared with HFrEF patients with other QRS morphologies (71). Moreover, a meta-analysis showed effect of CRT in NYHA class 1 patients, suggesting that CRT may also be beneficial in earlier stages of HF (72).

Currently, however, the main challenge with selection of patients for CRT is the consistent high number of non-responders. About one third of patients show no clinical improvement and in some cases even aggravation of symptoms (73). In addition, application of CRT in patients with narrow QRS (<130 ms) increased mortality compared to controls (74) and this

study was the reason why ESC guidelines changed recommendation for lower limit QRS duration from 120 to 130 ms. Since the therapy is also costly and the risk of serious device-related complications is significant, there is need for better selection criteria.

Several factors are known to affect the likelihood of response. Female gender, longer QRS duration, non-ischemic etiology and absence of scar are all predictors of favorable response. Moreover, LBBB morphology in ECG responds better than non-LBBB morphology, but there is still debate whether QRS duration or morphology is most important (75-79). Recent studies suggest the existence of a "point of no return" where patients with very depressed systolic function are likely not to respond (80, 81). In addition to total scar burden, there has been special attention towards scar in the LV posterolateral wall, which has been shown to be an independent predictor of non-response in several studies (82-85). This has been attributed to failure of efficient pacing delivery from the LV lead and it has been suggested that response can be achieved when optimizing LV lead position (86, 87). One study, however, found that the benefit of CRT with LV lateral wall scar was low, also when applying pacing in viable myocardium (88). Furthermore, as shown in mathematical simulation studies, decreased contractility in the LV posterolateral wall may reduce septal rebound stretch and improve septal shortening in LBBB (41), possibly indicating less potential for improvement of septal function with CRT (42). Therefore, there is need to improve understanding on how myocardial scar and, in particular, LV lateral wall scar affects LV function and abnormal septal motion in LBBB.

There has been numerous attempts to improve selection criteria for CRT and the primary focus has been echocardiographic indices of dyssynchrony. In fact, several timing-based indices were tested and proved useful in single-center studies (36, 37, 89). Nevertheless, when tested in a multicenter setting, none of the indices proved useful over current guidelines (90). This has in part been attributed to technical and methodological challenges, but evolving evidence has suggested that timing indices may be suboptimal measures of electromechanical dyssynchrony amenable to CRT (91, 92). Moreover, timing indices are sensitive to non-electrical causes of LV dyssynchrony (1, 3). This has led to new ways to assess dyssynchrony. In this regard, our group developed a method to differentiate different etiologies of dyssynchrony by onset of active myocardial force generation (93). More recently, focus has changed towards assessing specific contraction patterns that are associated with electromechanical dyssynchrony. In particular, there has been focus on the abnormal septal contraction pattern in LBBB (40-43, 81, 94, 95) and in favor of this concept it was shown that normalization of septal motion and perfusion after CRT is associated with positive response (58, 94, 96). Current guidelines, however, do not recommend any imaging parameter for dyssynchrony (59). Therefore, there is still need for new methods to predict CRT response.

To improve response rates in patients already receiving CRT, several approaches have been proposed. Targeted implantation of the LV lead at the site of latest mechanical activation as determined by speckle-tracking radial strain has showed improvement in the combined endpoint death and HF hospitalizations (97, 98). Multisite pacing, where the left ventricle is stimulated at multiple sites either by additional leads or a multipolar LV lead, is thought to provide more synchronous LV activation, but clinical benefit remains somewhat uncertain (99). In the adaptive CRT algorithm, LV pacing is fused with the intrinsic electrical activation given normal PR-interval. This allows a more physiological activation of the left ventricle and has proven clinical benefit (100). Furthermore, it has been relatively common to use echocardiography to optimize interventricular and, especially, AV delay in non-responders. The value of such approaches, however, remains uncertain (59).

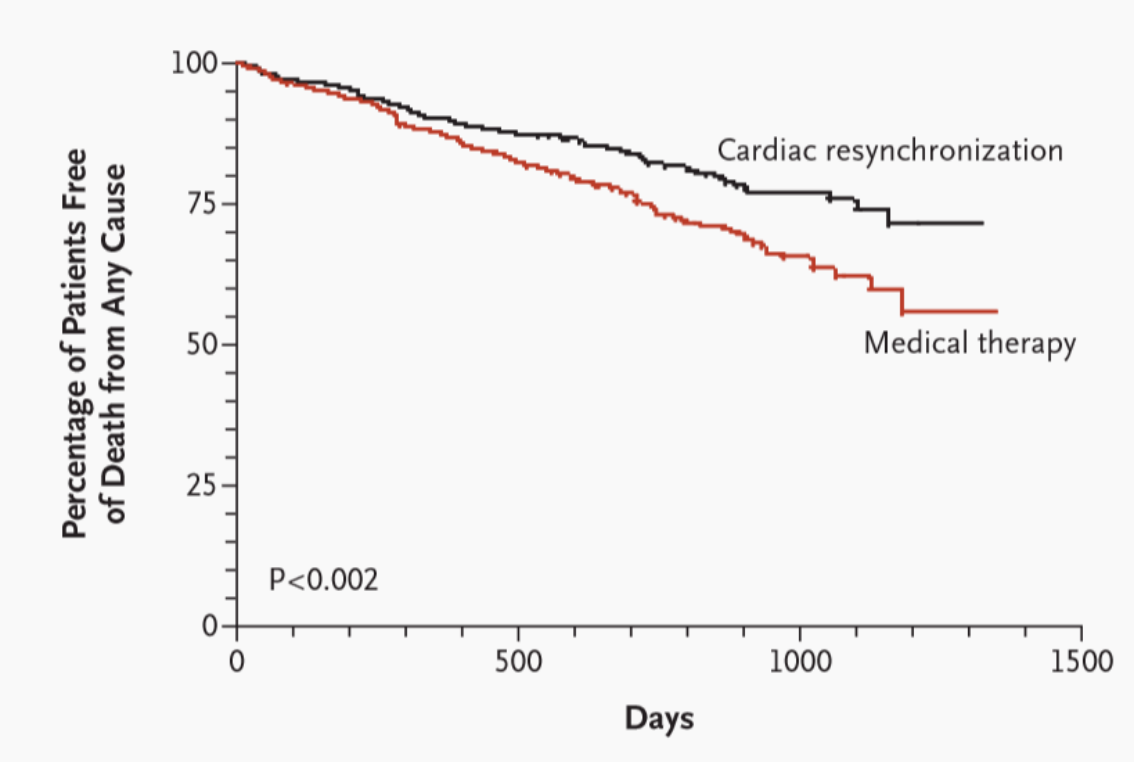

Figure 6. Survival with CRT as compared to optimal medical therapy alone. Reproduced with permission (67). Copyright Massachusetts Medical Society.

5. AIMS OF THESIS

General aims

To study regional and global LV function during LBBB to improve understanding of LV dyssynchrony on myocardial function and CRT response. We hypothesized that septal dysfunction is the main cause of LV systolic dysfunction in LBBB and that septal function can be restored by CRT leading to improved LV function, provided viable septal myocardium. Furthermore, we postulated that septal dysfunction in LBBB depends on interaction with the late-activate LV lateral wall and that the dyssynchronous ventricle is hypersensitive to increased afterload.

Specific aims

1. To determine the effect of increased afterload on regional and global LV function in LBBB.
2. To understand septal-to-lateral wall interaction and, in particular, the effect of LV lateral wall scar in LBBB.
3. To test the hypothesis that septal dysfunction, in the presence of viable septal myocardium and compensatory LV lateral wall hyperfunction, predicts response to CRT in a prospective multicenter study.

6. MATERIAL

Experimental studies

Paper 1

Eight anesthetized mongrel dogs of either sex and body weight of 34±2 kg were studied. LBBB was induced by radiofrequency ablation and afterload increased by constriction of the ascending aorta.

Paper 2

Ten anesthetized mongrel dogs of either sex and body weight of 40±4 kg were studied. LBBB was induced by radiofrequency ablation and ischemia induced by occlusion of the circumflex coronary artery (CX) (n=10) and left anterior descending coronary artery (LAD) (n=6).

The studies were approved by the National Animal Experimentation Board and the animals were supplied by the Center for Comparative Medicine (Oslo University Hospital, Rikshospitalet, Oslo, Norway).

Clinical studies

Paper 1

Eleven LBBB patients (age 62±8 years, 6 females) with preserved LV systolic function and without coronary artery disease were recruited through an outpatient cardiology practice. Additionally, 11 age-matched controls (age 60±10 years, 6 females) were recruited through voluntarily enrollment in the community. Afterload was temporarily increased by combining pneumatic extremity constrictors and handgrip exercise. Strain and LVEF were measured by echocardiography during baseline and increased afterload.

Paper 2

Forty heart failure patients with LBBB were studied by echocardiography. Most patients (n=35) also underwent late gadolinium enhancement cardiac magnetic resonance imaging (LGE-CMR) to evaluate the presence of myocardial scar. Twenty patients had ischemic cardiomyopathy (10 with anteroseptal scar and 10 with posterolateral scar) and 20 patients had non-ischemic cardiomyopathy. All patients were in sinus rhythm with typical LBBB configuration. All included patients were participating in ongoing CRT studies at Oslo University Hospital (n=31) and University Hospitals Leuven (n=9). The vast majority (36 of 40 patients) participated in the prospective study described in the next section.

Paper 3

Two hundred and thirty-six HF patients referred for CRT implantation were prospectively included at Oslo University Hospital (n=101), University Hospitals Leuven (n=50), Rennes University Hospital (n=71), OLV Hospital Aalst (n=11) and Karolinska University Hospital (n=3). In the study period, there were about 200 CRT implantations in Oslo, 300 in Rennes and 120 in Leuven. Therefore, approximately 35% of implanted patients in the main contributing centers were included. Inclusion criterion was indication for CRT according to 2013 ESC guidelines (5). Exclusion criteria were recent myocardial infarction or coronary artery bypass surgery, post heart transplantation, implanted left ventricular assist device, severe aortic stenosis, uncorrected congenital heart disease or impossibility to obtain LV volumes by echocardiography. Thirty-six patients were lost to follow-up due to study withdrawal (n=4), lack of echocardiographic data (n=7), endocarditis followed by lead extraction (n=1) or CRT not implanted (n=24). Hence, 200 patients were available for analysis. All patients underwent echocardiography and feasible patients (n=125) underwent LGE-CMR viability assessment prior to CRT implantation. Echocardiography was repeated at 7±1 months follow-up and survival assessed at 35±11 months follow-up.

The clinical studies were approved by the Regional Ethical Committee and written, informed consent was obtained from all study participants.

7. METHODS

Experimental studies (Paper 1-2)

Animal preparation

Experiments in paper 1 were performed prior to commencement of this PhD, while the series of experiments in paper 2 was performed in the period 2016-2018. For both series, we used a canine model allowing detailed hemodynamic measurements. The model is well-established and has been used by our group for many years (101-103). All experiments were performed by our research group at the Institute for Surgical Research, Oslo University Hospital, Rikshospitalet, Oslo, Norway.

First, the animals were anesthetized by either barbiturates and opioids (thiopentone 25 mg/kg and morphine 100 mg IV, followed by infusion of morphine 50 to 100 mg/h and pentobarbital 50 mg IV every hour) or propofol and opioids (single dose methadone 0.2 mg/kg, followed by propofol 3-4 mg/kg and a bolus of fentanyl 2-3 µg/kg, thereafter continuous infusion of propofol 0.2-1 mg/kg/min and fentanyl 5-40 µg/kg/hour). Anesthetic regime in our lab was changed from barbiturates to propofol in the period between the last experiments in the first paper. This was done after consultation with the Faculty of Veterinary Medicine at the Norwegian University of Life Sciences and the intention was to establish an easier controllable regime with less risk of irreversible overdosing. It should be noted, however, that both regimes have cardiodepressive effects with negative consequences for LV function.

After induction of general anesthesia the animals underwent endotracheal intubation with ventilation through a respirator. ECG was monitored from limb leads. Arterial and venous accesses were made through femoral and carotid vessel incisions followed by insertion of LV and aortic pressure catheters. The heart was accessed through a median sternotomy and the pericardium was split from apex to base. After instrumentation with crystals, right atrial pacemaker lead and left atrial (LA) pressure catheters, the pericardium was loosely resutured. Body temperature and arterial blood gas samples were regularly checked to avoid hypothermia and ensure adequate ventilation. Effect of anesthesia was regularly evaluated by assessment of hemodynamic parameters, interdigital reflex and tone. At the end of the experiment, animals were euthanized by an intracardiac injection of pentobarbital. All recordings were performed with the respirator temporarily switched off.

Pressures

Pressures were measured by micromanometer-tipped catheters (MPC-500, Millar Instruments Inc., Houston, Texas). To adjust for the problem with drifting, LV and LA

micromanometers were zero-referenced to LA pressure measured by a fluid-filled catheter for each recording. This was done during prolonged diastasis after an extrasystolic beat.

Sonomicrometry and regional electromyograms

LV dimensions were measured by sonomicrometry using piezoelectric crystals (Sonometrics Corporation, London, Ontario, Canada), which is considered gold standard for assessment of LV deformation. Septal, anterior, lateral and posterior 2 mm wide crystals were implanted subendocardially in the mid-equatorial plane in the left ventricle and combined with bipolar electrodes for measurement of intramyocardial electromyograms (IM-EMG) (Figure 7). Additionally, 3 mm wide basal and apical crystals were implanted for LV volume measurement using a three-axis ellipsoid model (104). Crystal positioning was optimized in the longitudinal and circumferential plane by checking the distance to other crystals. True subendocardial position in the radial plane, however, may be technically challenging and is difficult to check after implantation. An important consequence of a more epicardial crystal position is the inclusion of myocardium in the LV volume calculation, which gives too large volumes with false low LVEF. Furthermore, a segmental crystal pair with one crystal in a more epicardial position leads to an error in segmental deformation analysis as both wall thickening and shortening are included. Such error is most important when there is short distance between the crystals. Circumferential segment lengths were used to report segmental data. Sample rate was 200 Hz resulting in a temporal resolution of 5 ms.

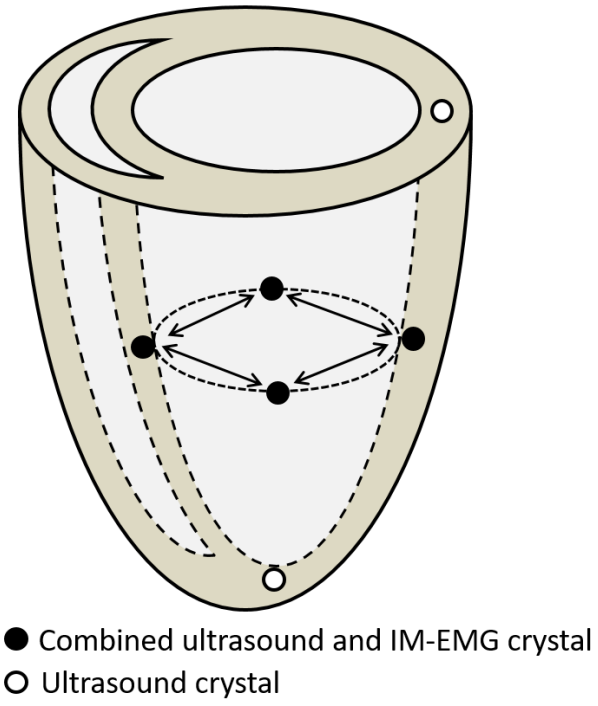

Figure 7. Placement of myocardial crystals. Arrows indicate circumferential segments used for measurements. Modified from Gjesdal et al. (103). IM-EMG = intramyocardial electromyogram.

Induction of LBBB

LBBB was induced by radiofrequency ablation (Celsius Catheter, Biosense Webster, Inc) as previously described at a location two thirds from the atrial and one third from the ventricular signal (103). Stable LBBB was ensured by at least 20 minutes observation prior to start of recordings.

Radiofrequency ablation is known as an adequate experimental model for LBBB and has been used by leading groups in the field (23, 105). It provides a stable LBBB activation pattern with similar LV deformation as seen in many patients. It does not, however, account for the heterogeneity in a mixed patient population and, importantly, in our acute model effects of long-standing LBBB activation pattern such as adverse LV remodeling is not taken into account. LBBB activation pattern may also be induced by RV free wall pacing (56) and one advantage of such method is the opportunity to switch on RV pacing and obtain immediate effects of dyssynchrony without the potential bias of cardiovascular deterioration between measurements. Nevertheless, for the present studies, we chose to use radiofrequency ablation as this probably resembles the clinical condition in LBBB patients most closely.

Elevation of afterload (Paper 1)

An inflatable silicon constrictor was placed around the ascending aorta. By inflating the constrictor, LV afterload was immediately increased. This allowed us to study segmental and global effects of beat-to-beat changes in LV afterload with minimal influence of compensatory reflexes.

LV lateral wall and septal ischemia (Paper 2)

To obtain LV lateral wall ischemia, we occluded the proximal part of CX (n=10) and to obtain septal ischemia we occluded the proximal part of LAD (n=6). The presence of adequate segmental ischemia was determined by sudden reduction in systolic shortening and increased post-systolic shortening (49). In the first five animals (CX occlusion n=5, LAD occlusion n=1), we used an adjustable extravascular occluder cuff which was attached around the artery. For the last five experiments, we changed the protocol and, instead, performed a coronary angiogram followed by intravascular balloon inflation with percutaneous coronary intervention technique. The reason for protocol change was to optimize the location of coronary occlusion and to enable occlusion of septal collaterals if needed, as proximal LAD occlusion may not always be sufficient to create septal ischemia. In fact, in one animal the posterior descending coronary artery was occluded simultaneously with LAD to obtain adequate septal ischemia. Furthermore, the new protocol was considered less hazardous for the animal as the technically challenging dissection of the CX

was avoided. In animals with occlusion of both arteries (n=6), we occluded the LAD first in 4 animals and the CX first in 2 animals to reduce the potential bias from preconditioning. Moreover, we took care to assure complete reperfusion and recovery of regional and global LV function prior to the next occlusion.

Clinical studies (Paper 1-3)

Echocardiography

All echocardiograms were performed with a Vivid E9 or E95 scanner (GE Vingmed, Horten, Norway). Recordings included two-dimensional (2D) grey-scale images from the parasternal and apical LV views and Doppler echocardiography to assess valvular function. Images were stored for off-line analysis. Ventricular volumes and LVEF were calculated by biplane Simpson's method as the average of three heartbeats. LV longitudinal strain was assessed by speckle-tracking echocardiography in apical views. Average frame rate per second was 59±6 in paper 1, 60±9 in paper 2 and 66±11 in paper 3. Brachial arterial blood pressure was measured at least twice immediately prior to the echocardiographic examination with the patient in supine position. Together with Camilla Kjellstad Larsen, the author of this thesis performed the vast majority of echocardiograms in patients and controls in Oslo.

Elevation of afterload (Paper 1)

Afterload was elevated by a combined method including isometric handgrip exercise (80% of maximum voluntary contraction) and inflatable cuffs around the right upper and the two lower extremities (Figure 8). Cuffs were inflated for periods of 30 seconds, which caused increase in total peripheral resistance. Simultaneously, the control subject performed isometric handgrip exercise (106). Blood pressure, heart rate and echocardiographic images were recorded continuously before, during and after the 30-second experiment. A photoplethysmographic pressure recording device (Finometer, FMS Finapres Medical System, Amsterdam, the Netherlands) placed on the left hand was used for blood pressure measurements. The device was calibrated against brachial arterial cuff pressure. The combined method (cuff inflation and handgrip exercise) was chosen based on results from a pilot study where blood pressure increase was larger with both methods combined than with any of them alone. Importantly, the intervention does not purely alter afterload as sympaticoadrenal tone is increased with effects on contractility and preload (106).

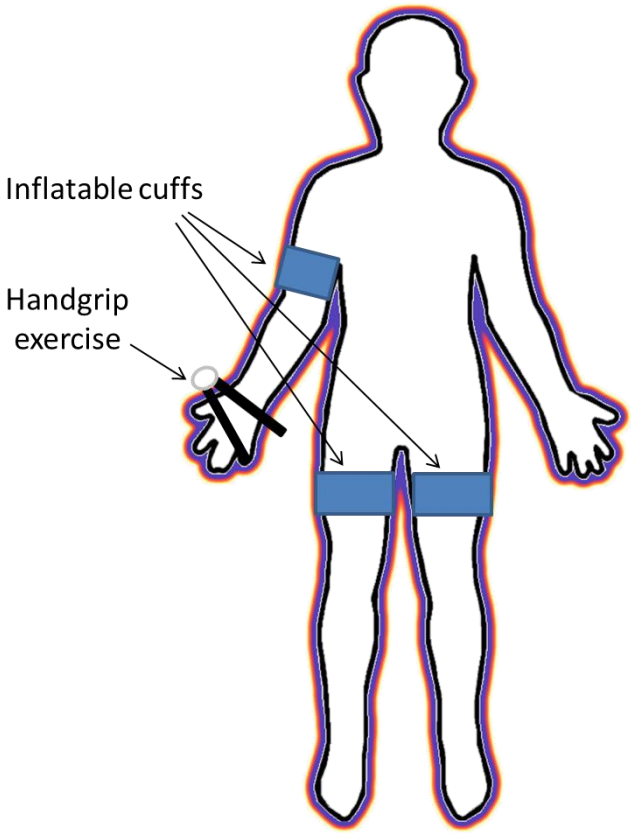

Figure 8. Experiment setup clinical study paper 1.

LGE-CMR (Paper 2-3)

Eligible patients (n=125) were scanned with a 1.5 or 3.0 Tesla unit (Aera, Skyra or Verio, Siemens, Erlangen, Germany, Ingenia, Philips Healthcare, Best, The Netherlands or Signa HDXT, GE, Boston, US). Main reasons for not undergoing LGE-CMR were previously implanted pacemaker or ICD (n=42) and reduced renal function (n=22) (patients with estimated glomerular filtration rate <45 ml/min/1.73m^2 were examined without contrast). Long- and short-axis LGE images were obtained at steady state after intravenous injection of either 0.15 or 0.20 mmol/kg gadoterate meglumine (Doteram™, Guerbet, Villepinte, France) or 0.15 mmol/kg gadobenate dimeglumine (MultiHance®, Bracco, Milan, Italy).

CRT implantation (Paper 3)

The decision to implant CRT was based on current ESC guidelines with final decision made by the responsible electrophysiologist. Coronary venography was used to guide implantation. Otherwise, implantation procedure and device manufacturer were according to clinical routine at the different institutions. All devices were programmed in conventional biventricular pacing mode and retested prior to hospital discharge.

Data analysis

i. Experimental data

General considerations

All measurements were obtained during sinus rhythm or right atrial pacing when necessary to obtain a stable heart rate. The average of three consecutive heart beats were used with the exception of afterload interventions where beat-to-beat changes were studied. During afterload increase, measurements were done within the first seconds after onset aortic constriction. During ischemia, measurements were done after 61±16 seconds of CX occlusion and after 42±16 seconds of LAD occlusion. The author of this thesis performed all data analysis.

Definition of end-diastole and end-systole

Commonly used definitions of end-diastole include onset QRS or peak R in the ECG, mitral valve closure and peak LV volume. However, due to regional differences in electromechanical activation, the definition of end-diastole is particularly challenging during LBBB. Peak R may be difficult to determine and mitral valve closure occurs somewhat after onset septal shortening as the first part of septal preejection shortening contributes to mitral valve closure (107). In the present experimental studies, our purpose was to study regional function during LBBB with special focus on septal function. Therefore, we chose to define end-diastole as onset septal shortening following septal electrical activation as determined by the IM-EMG. This, however, means the LV lateral wall was not yet electrically activated during end-diastole.

End-systole was set to aortic valve closure which was defined as peak rate of LVP decay (LV dP/dt_{min}).

Segmental myocardial deformation

Septal and LV lateral wall systolic shortening were measured as end-diastolic minus end-systolic segment length. Septal preejection shortening and rebound stretch were measured as indicated in Figure 3C while septal ejection shortening was defined as septal shortening during LV ejection. LV lateral wall preejection lengthening was defined as the early-systolic stretch occurring simultaneously to septal preejection shortening as can be seen in Figure 3C.

Segmental myocardial work

Invasive LVP and segment lengths from sonomicrometry were used to calculate segmental myocardial work as the pressure-segment length loop area. Work performed during segmental shortening (counterclockwise rotation of the pressure-segment length loop) was considered positive, whereas work performed during segmental elongation (clockwise rotation of the pressure-segment length loop) was considered negative. Net work was given as the sum of positive and negative work. Segmental length (absolute dimension) was used rather than strain (relative dimension) since this provides a more precise estimate of true work.

ii. Clinical data

The author of this thesis analyzed all echocardiographic data with exception of LV volumes in paper 3 and septal flash/apical rocking. Of note, work in paper 3 was analyzed without knowledge of volumetric data. CMR data was analyzed by two co-authors in Oslo. In paper 1, heart beats were analyzed immediately prior to the intervention and during maximum increase in systolic blood pressure.

Definition of end-diastole

Similar to the experimental studies, we defined end-diastole as onset septal shortening following onset QRS as determined by the ECG.

Myocardial strain

Longitudinal strain was measured by speckle-tracking echocardiography from the three apical views using an 18-segment model (Echopac version 202, GE Vingmed Ultrasound, Horten, Norway). The Q-analysis tool was used to manually delineate the endocardium and create a region of interest, which was adjusted to achieve optimal tracking of the myocardium. Special care was taken to avoid tracking the pericardium. Independent of software recommendation, all segments were checked carefully to ensure sufficient tracking quality. Segments that were poorly tracked despite repeated adjustments, were excluded. If more than one segment per view was excluded, global values were not given (108). In patients with irregular heart rhythm, beats with approximately average heart rate were used for analysis. Septal and LV lateral wall strain was obtained from septal and LV lateral wall segments in the apical 4-chamber view as described in the respective papers. Septal preejection shortening, rebound stretch and ejection shortening as well as segmental systolic shortening were defined as in the experimental study. Longitudinal strain was chosen over circumferential and radial strain due to its superior feasibility and reproducibility as well as its more frequent use. This, however, may potentially represent a

limitation as circumferential and radial strain may be more sensitive for dyssynchrony (109, 110). For simplicity, all strain values were given as absolute values.

Segmental non-invasive myocardial work index

As previously explained, the recent innovation of a non-invasive estimate of the LVP curve has made it possible to calculate an index of segmental myocardial work based on pressure-strain loop analysis. The method was innovated in our lab and validated against invasive LVP by micromanometer and dimensions by sonomicrometry (50).

First, a large number of invasively measured LVP traces were sampled. Thereafter, the isovolumic and ejection phases as well as peak LVP was normalized to create an average reference curve. The reference curve is adjusted to the individual patient by adding peak LVP (usually given as brachial systolic cuff pressure) and valvular events by echocardiography (provides timing of isovolumic and ejection phases). It is important to emphasize that the curve is only validated for pressure-strain loop analysis so that it cannot be used to calculate peak rate of rise or fall in LVP or diastolic pressures. Moreover, during conditions like aortic stenosis, where peak LVP is substantially different from peak aortic pressure, the method cannot be used unless the aortic pressure gradient is taken into account (50).

The myocardial work index (mmHg·%) is calculated by multiplying the rate of segmental shortening (derived from strain) with instantaneous LVP from the individually adjusted reference curve, which gives a measure of instantaneous power. This is integrated over time from mitral valve closure to mitral valve opening and the result is work performed during systole, which is similar to the area of the pressure-strain loop. The minor difference is that the myocardial work index does not subtract the negative work performed on the left ventricle during diastole when blood enters and stretches the LV walls. This work is mostly performed by the right ventricle and left atrium and as diastolic pressures are far lower than systolic pressures, such a small amount of work is usually negligible.

In the present studies, myocardial work was calculated semiautomatically with Echopac version 202 (GE Vingmed Ultrasound, Horten, Norway) using longitudinal strain from speckle-tracking echocardiography in the same 18-segment model as described in the previous section. Valvular events were defined in the apical 3-chamber view according to default software setting or, if the aortic valve was not sufficiently visualized, by Doppler echocardiography (111).

Septal and LV lateral wall work was measured from septal and LV lateral wall segments in the apical 4-chamber view as described in the papers. In paper 3, the lateral wall-to-septal (LW-S) work difference was calculated as LV lateral wall work minus septal work and was feasible in 98% of patients. Global work was measured as average of all 18 segments (similar to global longitudinal strain). As with strain, global values were not given if more than one

segment was excluded in a single view. Positive, negative and net work was defined similar as in the experimental studies.

Inter- and intraobserver variability for myocardial work has been tested in patients with LBBB and in other patient populations with good results (50, 112, 113). Intercenter variability, however, has to our knowledge never been examined and, thus, we performed an intercenter variability study in 38 randomly selected patients.

Alternative approaches (Paper 3)

Septal flash (38) and apical rocking (39) were assessed in Leuven by two experienced readers. In cases of disagreement (26 of 200 for septal flash and 28 of 200 for apical rocking), a final consensus reading was performed by a third reader. Septal flash was defined as preejection septal shortening or rapid leftward septal motion immediately after onset QRS and was assessed visually in apical 2D images or, when in doubt, with longitudinal strain or M-mode in parasternal views. Apical rocking was defined as a transverse rightward motion of the apex immediately after onset QRS, followed by a leftward motion of the apex during ejection. It was assessed visually in apical 2D images (94). Systolic stretch index (114) was calculated from longitudinal strain traces in the apical 4-chamber view as the sum of early-systolic stretch in the LV lateral wall and septal systolic stretch (rebound stretch plus late-systolic septal stretch).

Myocardial scar (Paper 2-3)

First, LGE-CMR images were assessed visually by an experienced CMR radiologist to determine the presence of macroscopic myocardial fibrosis. If fibrosis was present, Segment software v2.0 R5270 (115) was used for semiautomatically quantification of scar size using the automatic algorithm EWA (expectation maximization, weighted intensity, a priori information). Polar maps were constructed using a 17-segment model. Myocardial scar was reported regionally as percentage of total amount of tissue per wall and globally as percentage of total amount of tissue in the left ventricle. Scars were analysed and reported the same way independent of ischemic or other cause.

Primary endpoint (Paper 3)

Primary endpoint in paper 3 was reverse remodeling at 7±1 months follow-up defined as ≥15% reduction in LV end-systolic volume index. Volumes were, as previously mentioned, measured by the biplane Simpson method using echocardiographic images from the apical 2- and 4-chamber view. These measurements, however, are afflicted by significant inter- and intraobserver variability (116), which may affect the decision of CRT response or not for a number of patients. To minimize the impact of such variability, all volumes were measured at three different locations (Rennes, Leuven and Oslo) by different observers who were

blinded to work data. In cases of disagreement on response, a majority decision was made. Average of agreeing volumes was used for volumes as a continuous variable. For further discussion on the use of LV volumes as endpoint, please see the discussion section.

Secondary endpoint (Paper 3)

Death of any cause or heart transplantation constituted the secondary endpoint. The secondary endpoint was assessed at 35±11 months follow-up. Initially, we planned to include HF hospitalizations in the secondary endpoint, but data on the cause of hospitalization were unfortunately insufficient in a significant number of patients.

Statistics

Continuous values are presented as mean±standard deviation or confidence intervals (CI). Comparisons within one group was performed by paired sample t-test, whereas comparisons between two groups were performed using independent sample t-test or chi-square test as appropriate. In paper 1, significance of the interaction effect from an analysis of variance was reported to highlight differences in afterload effect between LBBB and control conditions. In paper 3, linear regression (univariate and multivariate) was used to identify predictors of CRT response and receiver operating characteristic (ROC) curves with area under the curve (AUC) values were used to determine test properties. The assessment of myocardial work and viability was combined by using logistic regression to calculate probability of response. This parameter was thereafter used for construction of ROC curves. The DeLong method or, when more appropriate (117), the Hanley & McNeil method (MedCalc Software 2019) were used to compare ROC curves. Survival data are presented as hazard ratios (Cox regression and Kaplan Meier curves with log-rank test). For reproducibility, we used Bland-Altman plots, Pearson correlation, intra-class correlation coefficient (ICC) and Cohen's kappa. In general, a p-value of <0.05 was considered statistically significant. However, when testing in two groups or if comparisons were not orthogonal, we applied Bonferroni correction so that only a p-value of <0.025 was significant. SPSS version 25.0 software (SPSS, IBM, Armonk, New York) was used for the analyses.

8. SUMMARY OF RESULTS

Paper 1

Clinical study

During intervention, systolic blood pressure increased with 38±12 mmHg in controls and 34±13 mmHg in LBBB patients (p=NS). This was accompanied by a moderate increase in heart rate in the two groups (20±11 in controls vs. 22±10 in LBBB patients, p=NS). In controls, the intervention reduced LVEF from 60±4% to 54±6% and global longitudinal strain (GLS) from 20.8±2.5% to 18.4±2.4% (both $p<0.01$). In LBBB patients, reduction in systolic function during increased afterload was substantially larger with LVEF decreasing from 56±6% to 42±7% and GLS from 17.1±2.2% to 12.4±1.8% (both $p<0.01$) (Figure 9). The absolute reduction in LVEF was 7% in controls and 14% in LBBB patients (95% CI: 3-10% and 11-17%, respectively; $p<0.01$). Similarly, the absolute reduction in GLS was 2.3% in controls and 4.7% in LBBB patients (95% CI: 1.0-3.6% and 3.7-5.7%, respectively; $p<0.01$).

Afterload hypersensitivity in patients with LBBB was attributed to reduction in septal function, which was further explored in the experimental model.

Experimental study

During control conditions, aortic constriction caused only moderate reductions in regional LV function. During LBBB, however, aortic constriction caused marked reduction in septal systolic shortening (1.2±0.5 to 0.0±0.8 mm, $p<0.02$). This was mainly due to reduced septal shortening or even lengthening in the ejection phase when LVP was at its peak and was reflected in the septal pressure-dimension loop (Figure 10). Septal work became net negative during increased afterload (78±171 to -161±160 mmHg·mm, $p<0.01$), which indicates complete loss of septal contribution to LV systolic function. There was no significant change in LV lateral wall shortening or work.

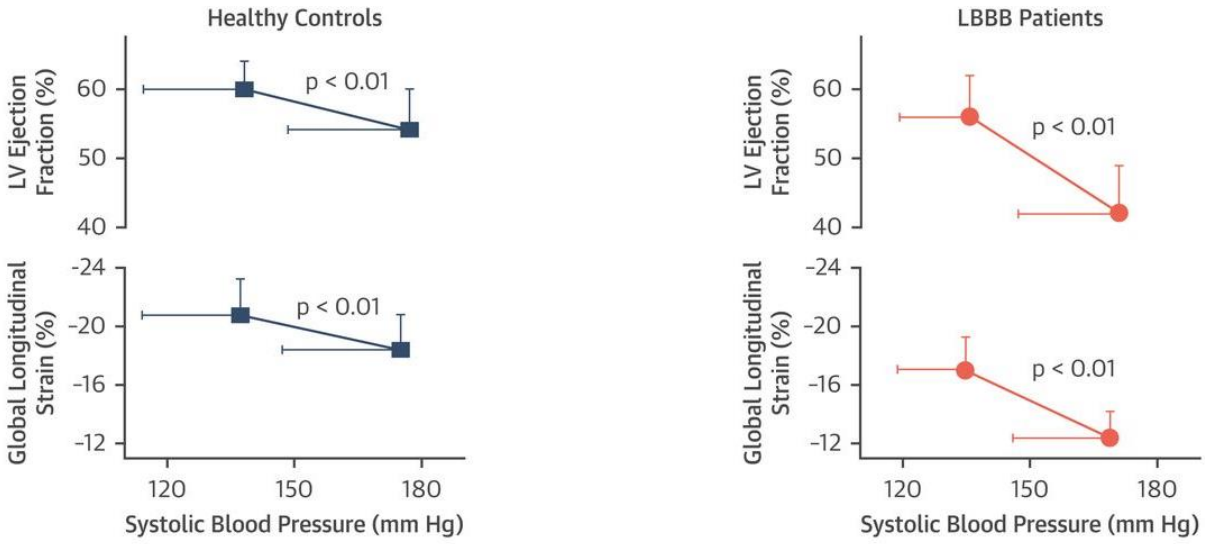

Figure 9. Clinical data. Response to increased afterload. During increased systolic blood pressure there is marked reduction in LV ejection fraction and global longitudinal strain among LBBB patients (right panel) which is significantly different from the moderate reduction seen in controls (left panel). Modified from Aalen et al. with permission (118). LBBB = left bundle branch block, LV = left ventricular.

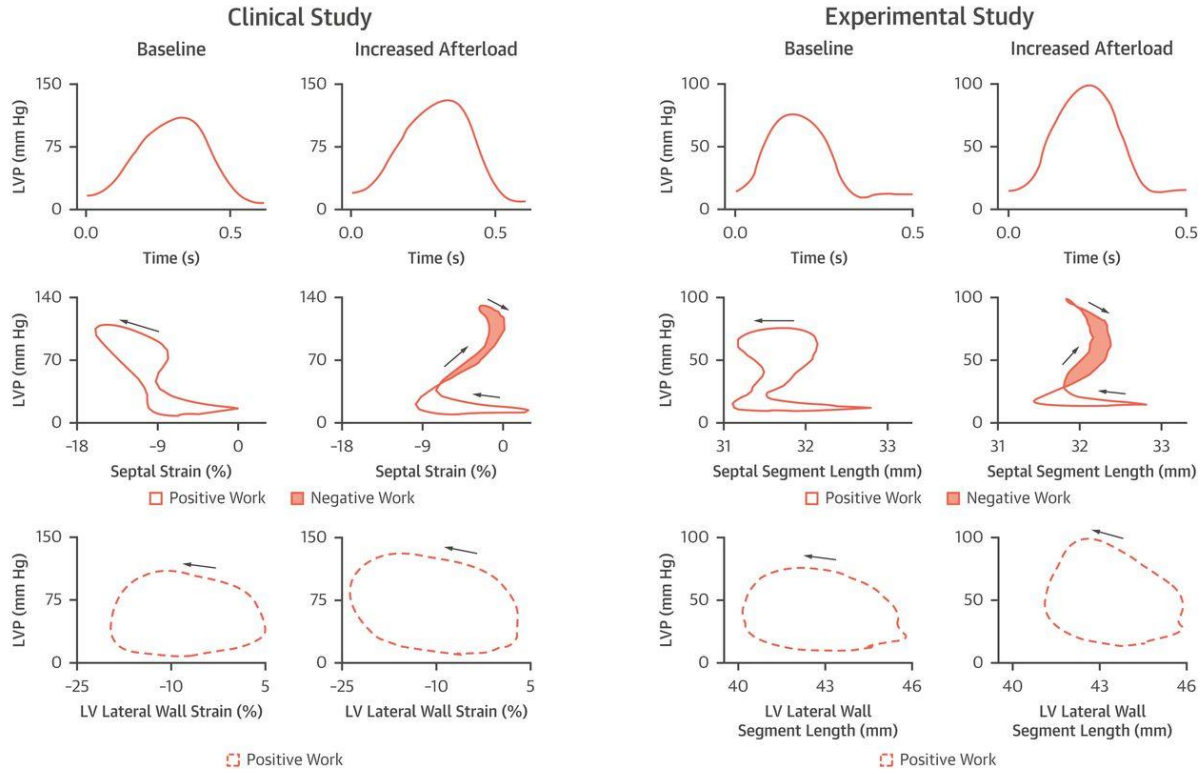

Figure 10. Pressure-strain loops from a representative LBBB patient (left) and pressure-segment length loops from a representative animal after induction of LBBB (right). Septal loops show reduced positive work already at baseline as indicated by a small loop area. During increased afterload septal dysfunction is aggravated with clockwise rotation indicating negative work. LV lateral wall work, on the other hand, is preserved. Reproduced with permission (118). LBBB = left bundle branch block, LV = left ventricular, LVP = left ventricular pressure.

Paper 2

Experimental study

Induction of LBBB was followed by abnormal septal motion with preejection shortening, rebound stretch and substantially reduced septal systolic shortening in all animals. During CX occlusion, LV lateral wall shortening decreased from 5.0±1.2 mm to 0.5±1.0 mm ($p<0.001$) and was accompanied by marked changes in septal deformation (Figure 11). Septal rebound stretch was markedly reduced (1.4±0.6 to 0.2±0.2 mm, $p<0.001$) and septal systolic shortening was restored to similar values as before induction of LBBB. Furthermore, there was a substantial increase in septal work from 5±62 to 108±47 mmHg·mm ($p<0.001$).

During LAD occlusion, we observed opposite changes in septal deformation. Septal rebound stretch increased and septal systolic shortening was substantially reduced (Figure 11).

QRS duration was unchanged during both CX and LAD occlusion.

Clinical study

Similar to the experimental study, patients with LBBB and posterolateral wall scars had severely depressed function in the LV lateral wall. This was accompanied by lack of septal rebound stretch and far better septal systolic shortening than non-ischemic LBBB patients (10.7±4.4 vs. 2.2±3.5%, $p<0.001$) (Figure 11). There were corresponding differences in LV lateral wall and septal work, where septal work on average exceeded LV lateral wall work in patients with posterolateral scars, which resulted in a negative LW-S work difference.

For LBBB patients with anteroseptal scars, we observed abnormal septal motion with similar rebound stretch and septal systolic shortening as non-ischemic patients (Figure 11).

There were no significant differences in LVEF or QRS duration between the three patient groups.

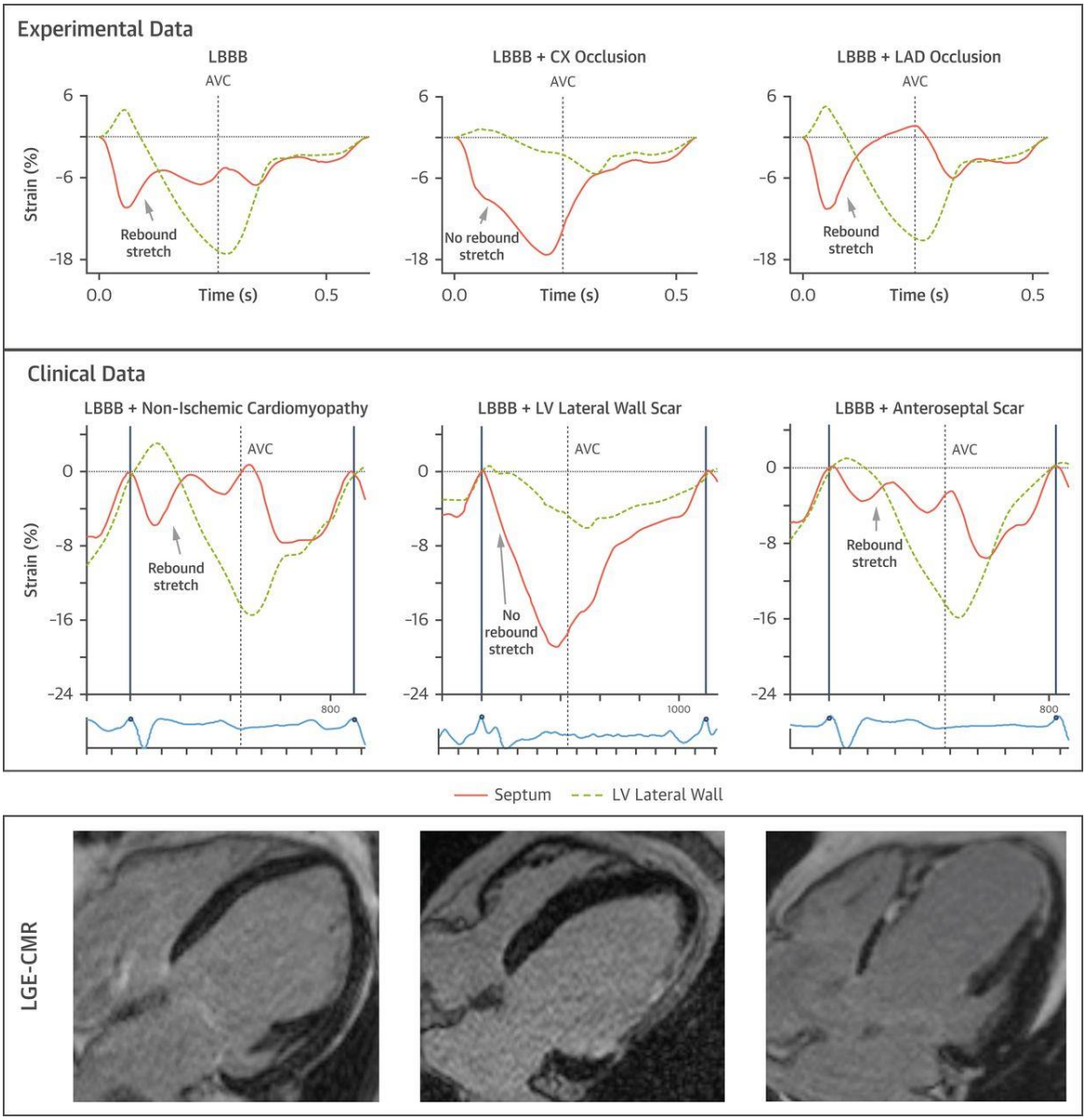

Figure 11. Upper panels show strain traces from a representative animal during LBBB, LBBB with CX occlusion and LBBB with LAD occlusion. Septal rebound stretch is lost and septal systolic shortening markedly improved with CX occlusion. Lower panels show strain traces and LGE-CMR images from three representative LBBB patients. Similar to the experimental data, there is no septal rebound stretch and instead close to normal septal deformation in the patient with LV lateral wall scar. Reproduced with permission (119). AVC = aortic valve closure, CX = circumflex coronary artery, LAD = left anterior descending coronary artery, LBBB = left bundle branch block, LGE-CMR = late gadolinium-enhanced cardiac magnetic resonance imaging, LV = left ventricular.

Paper 3

Sixty-eight percent of patients responded to CRT in terms of reverse remodeling. As expected female gender, sinus rhythm and non-ischemic cardiomyopathy were more common among responders.

Prior to CRT, there was more LV lateral wall work and less septal work in responders as compared to non-responders (Figure 12). This was reflected in a substantially larger LW-S work difference ($p<0.001$). After 6 months with CRT, LV lateral wall work was reduced and septal work increased, which abolished the LW-S work difference in both responders and non-responders. Among responders, however, reduction in LV lateral wall work was far exceeded by increased septal work leading to improved global systolic function. In non-responders, on the other hand, there were similar reduction in LV lateral wall work, but only a small increase in septal work resulting in no net benefit from CRT (Figure 12). In univariate linear regression analysis, there was correlation between reverse remodeling and LW-S work difference ($r=0.44$, $p<0.001$). Multivariate linear regression analysis including LW-S work difference, heart failure etiology (ischemic or non-ischemic), QRS duration and QRS morphology (LBBB or non-LBBB) revealed that LW-S work difference was an independent predictor of reverse remodeling ($p<0.001$). AUC for LW-S work difference for CRT response prediction was 0.77 (95% CI: 0.70-0.84) as compared with 0.56 for QRS morphology (95% CI: 0.47-0.64) and 0.54 (95% CI: 0.45-0.63) for QRS duration. A cut-off of 860 mmHg·% provided 83% sensitivity, 58% specificity, 80% positive predictive value, 63% negative predictive value and 75% accuracy for CRT response.

LGE-CMR was performed in 125 patients and scar was present in 61. Multivariate linear regression analysis including septal, inferior, anterior and LV lateral wall scar, found that only septal scar was an independent predictor of reverse remodeling ($p<0.05$). Furthermore, in multivariate analysis with septal scar, LW-S work difference, QRS duration and QRS morphology, only septal scar and LW-S work difference predicted reverse remodeling. A combined assessment of LW-S work difference and septal viability gave AUC 0.88 (95% CI: 0.81-0.95) for CRT response prediction and was similar in the subgroup of patients with QRS duration 120-150 ms. A cut-off of ≥725 provided 86% sensitivity, 84% specificity, 94% positive predictive value, 67% negative predictive value and 85% accuracy for CRT response.

The ROC-curve for LW-S work difference alone was somewhat better than systolic stretch index ($p<0.05$), but not significantly different from septal flash and apical rocking. The combined approach with work difference and viability, however, was superior to septal flash, apical rocking and systolic stretch index (all $p<0.025$).

Both LW-S work difference alone and combined with septal viability predicted reduced risk of heart transplantation or death at long-term follow-up (hazard ratio 0.36 (95% CI: 0.18-0.74) and 0.21 (95% CI: 0.072-0.61), respectively).

Intercenter variability for LW-S work difference was good with ICC 0.90 (95% CI: 0.84-0.94)) and average agreement for cut-off 860 mmHg·% of 89% (kappa range 0.65-0.85). Intercenter agreement for septal flash and apical rocking was moderate (68% (kappa range 0.16-0.46) and 70% (kappa range 0.25-0.69), respectively).

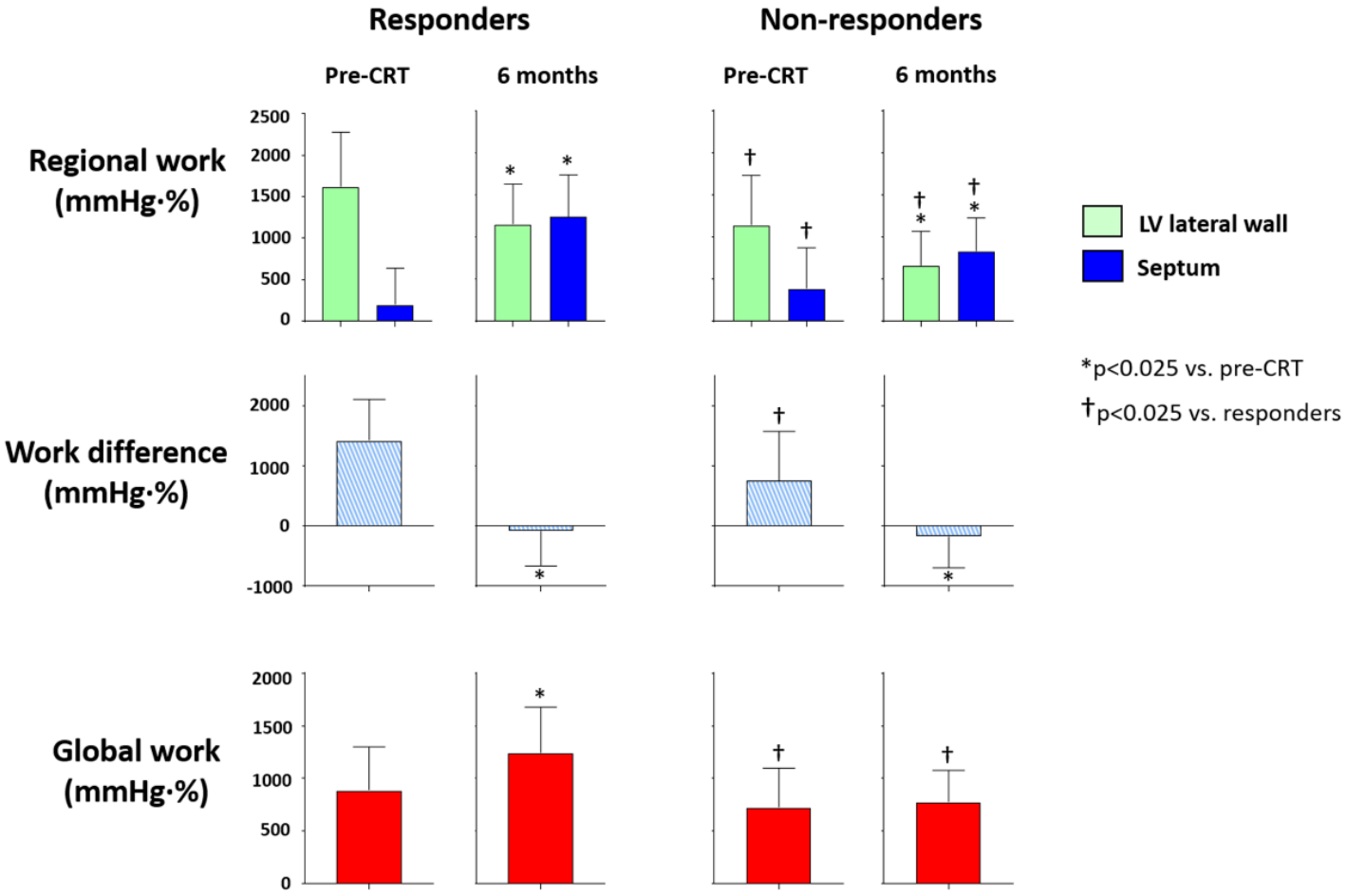

Figure 12. Work distribution in responders and non-responders before and after 6 months with CRT. Reproduced with permission (120). CRT = cardiac resynchronization therapy, LV = left ventricular.

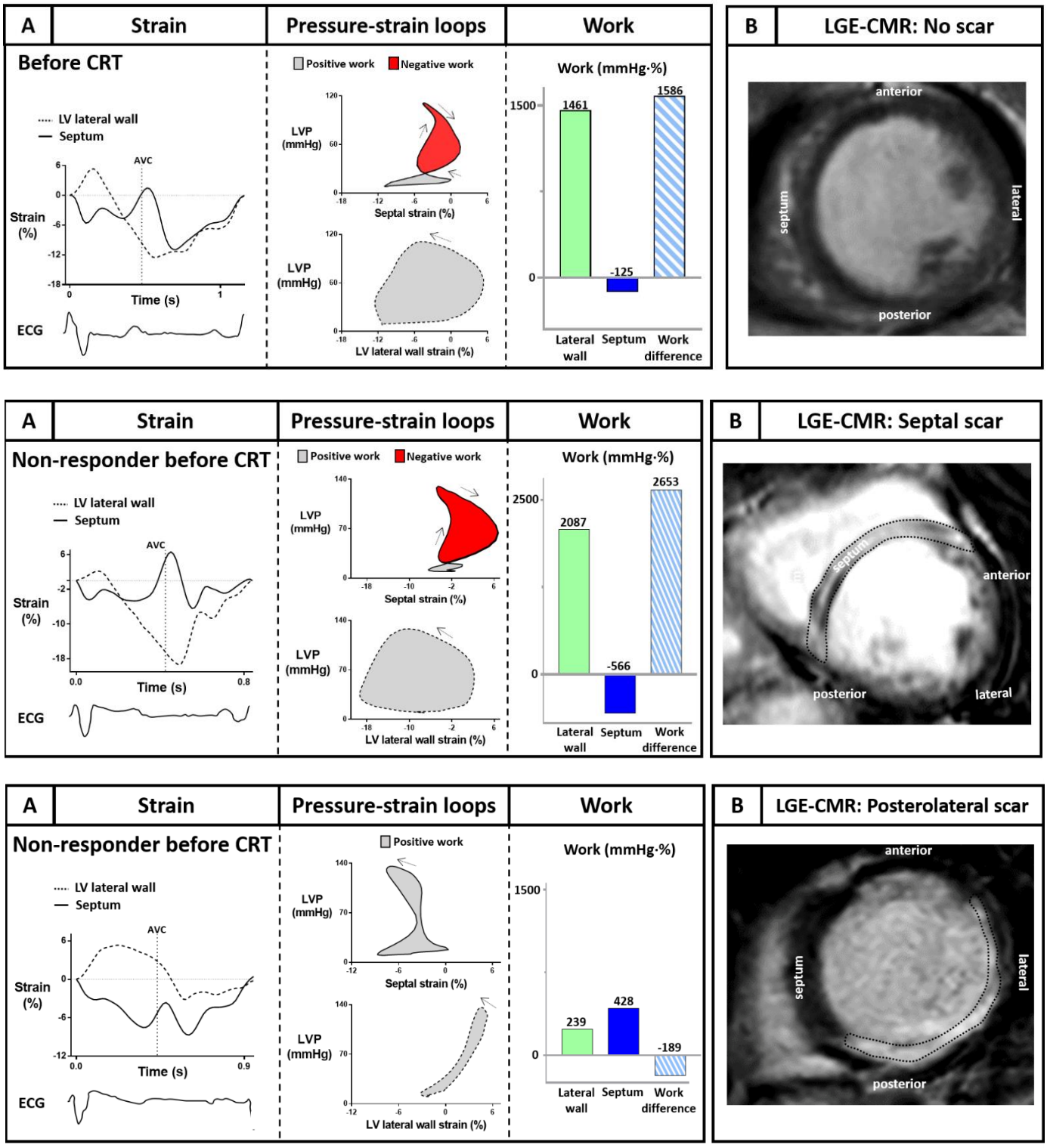

Figure 13. Three patients illustrating main study findings. Upper panels: Strain traces, pressure-strain loops and LGE-CMR images from a non-ischemic LBBB patient who became a super-responder to CRT. There is predominantly negative septal work as indicated by the red colored septal pressure-strain loop area and preserved LV lateral wall work as indicated by the large grey colored loop area. This gives a large lateral wall-to-septal work difference and together with septal viability, it indicates potential for recovery of septal function with CRT. Mid panels: Similar to the super-responder this LBBB patient showed predominantly negative septal

work and a large lateral wall-to-septal work difference. LGE-CMR, however, revealed extensive septal scarring with less potential for recovery of septal function and the patient became a non-responder. Lower panels: LBBB patient with posterolateral scar and therefore negative work difference indicating little potential for recovery of LV function with CRT. The patient became a non-responder. Modified from Aalen et al. with permission (120). AVC = aortic valve closure, CRT = cardiac resynchronization therapy, ECG = electrocardiogram, LBBB = left bundle branch block, LGE-CMR = LGE-CMR = late gadolinium-enhanced cardiac magnetic resonance imaging, LV = left ventricular, LVP = left ventricular pressure.

9. DISCUSSION

In the present thesis, we have studied different aspects of LV dyssynchrony with special focus on consequences for myocardial function and CRT response. In paper 1, we found that LBBB patients are prone to moderate acute elevations of systolic blood pressure as they showed marked worsening of septal function with subsequent reduction in LV systolic function. In paper 2, we showed that reduced septal function during LV dyssynchrony is closely related to viability and function of the LV lateral wall. Therefore, in animals with LBBB and LV lateral wall ischemia, septal function was partly restored. In paper 3, we showed that response to CRT depends on markedly reduced septal function which is not due to septal scar, but instead due to electromechanical dyssynchrony with compensatory increased function in the LV lateral wall. In total, our findings support the notion that septal dysfunction is a key mechanism for reduced LV systolic function during LBBB and, hence, septal function should be the main target for improving LV function with CRT.

The effect of afterload on left ventricular systolic function

In paper 1, we showed that healthy control subjects experienced moderate reductions in LVEF and GLS during increased afterload. This does not represent a true reduction in LV systolic function, but is rather in line with normal afterload dependency of myofiber shortening (121, 122). It has previously been shown that both LVEF and GLS are afterload dependent (101, 123, 124) and this should always be kept in mind when using such parameters to evaluate LV systolic function. In this context, myocardial work, which integrates afterload, showed better accuracy with reduced number of false positives compared to strain alone to identify acute coronary occlusion in patients with non-ST-elevation acute coronary syndrome (112). Moreover, Chan et al. recently found higher values of global myocardial work in hypertensive patients as controls, but no difference in LVEF or GLS. The findings suggest compensatory increased myocardial work to preserve LVEF in patients with hypertension and may contribute to improve understanding of LV remodeling and HF development in such patients (113). Currently, there is lot of attention towards cardiotoxicity in patients undergoing oncologic treatment. Specifically, several studies have looked into the use of GLS for detection of early-stage cardiotoxicity and found that a 10% to 15% relative reduction in GLS seems to be the most useful parameter to predict subsequent drop in LVEF and development of HF (125). In this regard, we found that among healthy controls participating in the clinical study in paper 1, there was an average relative reduction in GLS during elevated afterload of 12% and that GLS was reduced by more than 15% in three of eleven individuals (126). In contrast, global myocardial work was preserved or increased. The increase in systolic blood pressure was in the range of what can be seen in many patients during medical consultation (127). The finding suggests that a cut-

off of 15% reduction in GLS for cardiotoxicity may lead to false positives with the potential for unnecessary treatment and patient concern if blood pressure is not taken into consideration. The topic will be further explored in an ongoing study from our group.

It has previously been shown that hearts with reduced contractility are less tolerant to elevations of afterload (128, 129) and, furthermore, afterload-reducing treatment is a cornerstone in the treatment of HFrEF patients (59). As previously explained, both experimental and clinical studies have shown that LBBB itself causes reduced LV contractility (23-26). The findings in paper 1 supports this notion. Even though LVEF in LBBB patients was within normal limits and not significantly different from controls, there was significant difference in GLS which was lower in LBBB patients. Similar differences were seen with peak rate of LVP rise in the experimental study where animals served as their own controls. Therefore, one could argue that the finding of increased afterload sensitivity in LBBB patients was to be expected. The magnitude of the effect, however, could not be foreseen and the finding may have clinical implications.

Potential effects and implications of chronic elevated afterload in left bundle branch block

In paper 1, we studied the acute effect of afterload elevation within seconds after onset of the intervention. In clinical practice, we are most interested in the effect of chronic elevated afterload as seen in patients with arterial hypertension or aortic stenosis. There are important differences between acute and chronic afterload elevation. For example, the Anrep effect is an intrinsic myocardial autoregulation mechanism which leads to a compensatory increase in contractility when afterload is increased for several minutes (130). Therefore, one would expect the Anrep effect to partially counteract the reduction in LVEF and GLS if our intervention lasted for a longer period. Additionally, an acute intervention does not take into account LV remodeling in response to longstanding elevated afterload. In total, it is likely that the observed reduction in LVEF and GLS would be less in the setting of chronic elevated afterload.

A relevant clinical question is whether LBBB patients with arterial hypertension or aortic stenosis are more prone to HF development due to increased afterload sensitivity and whether this has implications for treatment of such patients. In the previously mentioned LIFE study, which followed patients with hypertension, echocardiography was performed in a subpopulation including 47 LBBB patients (131). There were no significant differences between LBBB patients and controls with regards to blood pressure, previous myocardial infarction or age. Systolic function, however, was reduced in LBBB patients both in terms of LVEF and stroke volume. Additionally, for the whole LIFE population (including 564 LBBB patients), there was no increased risk of myocardial infarction in LBBB patients, but still a

1.7-fold increased risk for HF hospitalization and 1.6-fold increased risk for cardiovascular death (22). These findings suggest hypertension and LBBB as a particularly negative combination with regard to HF development. This being said, we do not know how such a comparison would look in an otherwise similar normotensive population and, as previously explained, it has been shown that LBBB patients in general are more prone to HF development than patients with normal QRS duration. Moreover, it is not possible to rule out coexisting heart disease as a contributor to increased cardiovascular mortality and, in fact, for the whole LIFE population there was increased prevalence of previous cardiovascular disease among LBBB patients (33%) as compared to hypertensive patients with normal QRS duration (25%).

Another interesting finding is from the MADIT-CRT trial where LBBB patients treated with the afterload-reducing beta blocker carvedilol showed reduction in the combined endpoint HF hospitalizations and death compared to those treated with metoprolol, which has less effect on afterload (132). Furthermore, a recently published study on patients with aortic stenosis undergoing TAVR found improved LVEF after TAVR only in patients with pre-existing LBBB (133), possibly suggesting increased benefit from afterload reduction in LBBB patients.

At present, no specific treatment is recommended in asymptomatic patients with LBBB and preserved LV systolic function. Since development of HF is a significant problem in such patients (21, 134), it is important to identify and treat risk factors. If chronic afterload hypersensitivity can be proven, it may have consequences for antihypertensive treatment recommendations. Possibly, antihypertensive treatment should be initiated earlier and more aggressively than in patients with normal electrical conduction. There is need for future studies to address these questions.

Mechanisms of abnormal septal motion in left bundle branch block

Abnormal septal motion is the echocardiographic hallmark of LBBB and was first described in the early 1970s (34, 35, 135). Dillon et al. named the motion septal beaking and found that it was absent in selected patients with coronary artery disease (35). Renewed interest in abnormal septal motion was gained with the introduction of CRT in the 2000s. The rapid early-systolic color shift on color M-mode was named septal flash (38), which, as previously mentioned, has become a relatively well-known term in echocardiography. Numerous observational and retrospective studies have shown positive association between septal flash and CRT response (38, 94, 136-141), but septal flash has still not been tested in a randomized trial or included in CRT guidelines. Furthermore, there is no consistent definition of septal flash (142).

The first components of abnormal septal motion during LBBB are preejection septal shortening in the longitudinal and circumferential direction, sepal thickening in the radial direction and leftward septal motion (transverse motion). Immediately after, the opposite occurs with septal rebound stretch, septal thinning and paradoxical rightward septal motion. Towards end of systole there is premature termination of shortening and late-systolic septal stretch (2). The original definition of septal flash by Parsai et al. included both the leftward and the following paradoxical rightward septal motion (38), but more recently septal flash has been defined only as the leftward septal motion (143). Furthermore, preejection longitudinal shortening assessed by strain imaging is frequently counted as septal flash (143). Although this may seem like minor distinctions, it is of importance during certain conditions.

It was previously believed that right- and leftward septal motion were caused by delayed pressure build-up in the left ventricle. Rightward motion was caused by a transseptal pressure gradient in favor of the right ventricle so that the septum was forced leftwards like a passive membrane. As LVP finally exceeded RV pressure, the pressure gradient was reversed thereby causing rightward septal motion (144, 145). However, Gjesdal et al. and Remme et al. found that leftward septal motion had an active component as it occurred against rising LVP and a rising transseptal pressure gradient in favor of the left ventricle (103, 107). More recently, Walmsley et al. showed that leftward septal motion also has a passive component due to the early-activated RV free wall pulling on and straightening the septum (146). Furthermore, they found that during a scenario in which both the RV and LV free wall are late-activated (trifascicular block with combined RBBB and LBBB) the leftward septal motion would not occur, but there would still be preejection shortening and rebound stretch. These findings indicate that transverse septal motion compared to longitudinal and circumferential septal motion has a somewhat different underlying mechanism.

It was previously suggested by experimental and clinical studies (9, 42, 147) that septal rebound stretch is caused by contraction in the late-activated LV lateral wall. Leenders et al. found in a mathematical simulation study that rebound stretch is decreased by reduced LV lateral wall contractility and increased by reduced septal contractility (41). This is in line with the experimental study in paper 2 as well as the finding in patients with LV lateral wall scars and indicates that abnormal septal motion in LBBB is determined not only by the electrical conduction delay, but also by the balance of contractile forces in the septum and LV lateral wall. In paper 2, we showed that loss of LV lateral wall contractility also caused loss of paradoxical rightward septal motion, indicating that both septal rebound stretch and rightward septal motion depend on LV lateral wall function. This means that according to the chosen definition, septal flash may either include or not include assessment of LV lateral wall function. Assuming LV lateral wall contractility is a key determinant of LBBB-induced septal

dysfunction and recovery potential with CRT, it seems preferable that the term septal flash also includes rightward septal motion and rebound stretch.

Paper 1 is to our knowledge the first to show how abnormal septal motion in LBBB is strongly dependent on afterload and this has later been confirmed by Prinzen et al. (148). The finding suggests that blood pressure should be taken into account when evaluating patients for CRT based on abnormal septal motion.

Septal contractile function and its relation to left ventricular systolic function

In paper 1, septal work was about half the value of LV lateral wall work in LBBB patients during normal afterload. This difference was not reflected in LVEF, which was within normal limits and not significantly different from controls. GLS, however, was significantly reduced to subnormal values, which reflects reduced septal contribution to LV systolic function. It has previously been shown that uneven workload distribution with increased workload on the LV lateral wall may lead to LV remodeling with asymmetric hypertrophy (29). During increased afterload with subsequent reduction in LV systolic function, there was a further reduction of septal function. In fact, in the experimental study, septal work became net negative during elevated afterload, which means that septal contribution to LV systolic function was lost and instead the septum absorbed work performed by the LV free wall. Therefore, during LBBB and increased afterload, the workload asymmetry between the septum and LV lateral wall was aggravated and may be a mechanism of accelerated LV remodeling in patients with chronic elevated afterload.

In paper 3, workload asymmetry given as the difference in myocardial work between the LV lateral wall and septum (LW-S work difference) correlated with improvement in LV systolic function after CRT suggesting improved septal function as a main mechanism for CRT response. This was further supported by the observation that patients with reduced septal viability, and therefore with less potential for improvement in septal function, responded poorly. Moreover, patients with poor LV lateral wall function, as seen for example (but not solely) with posterolateral scars, showed less improvement with CRT. As previously mentioned, such finding has been attributed to failing of pacing delivery when the LV lead is positioned in a scar region. In accordance with the findings in paper 2, however, this could be explained by poor LV lateral wall contractions leading to less LBBB-induced impairment in septal function.

The LW-S work difference provides a comprehensive measure of the contractile disturbance in LBBB by including both the LBBB-induced reduction in septal function as well as LBBB-induced hyperfunction in the LV lateral wall. This implies that during severely reduced

function in both walls (as for example in end-stage HFrEF), LBBB is not likely to be the main cause of septal dysfunction and resynchronization is less likely to help.

Septal viability

In contrast to the considerable focus on posterolateral scars, the literature on septal scar in CRT recipients is scarce. One study of 23 patients receiving CRT showed that absence of septal scar was a strong predictor of CRT response (149), whereas another study of 50 patients showed that septal scar was associated with poor acute and long-term response (150). In the latter study, the authors suggest problems with placing the RV lead in the septum to be the underlying mechanism of non-response. However, the importance of RV pacing for CRT response is questionable as also LV only pacing improves LV systolic function (105, 151). In paper 3, we showed that septal scar was a strong predictor of non-response to CRT and propose reduced septal recovery potential as the main mechanism. Moreover, as indicated in paper 3, it may be impossible to separate septal dysfunction primarily due to scar from septal dysfunction primarily caused by dyssynchrony with echocardiography and, hence, the present findings support the use of LGE-CMR for evaluation of CRT candidates.

A substantial number of patients undergoing evaluation for CRT are not candidates for LGE-CMR due to already implanted pacemaker device or poor kidney function. In such patients, nuclear imaging may serve as an alternative modality for viability assessment. Septal viability assessment, however, may not be feasible as reduced septal perfusion and metabolism reflecting reduced septal work are typical features of LBBB-induced dyssynchrony (50, 54, 55). The topic is currently being investigated.

Cardiac resynchronization therapy response

Defining CRT response

On group level in randomized trials, CRT has favorable effects on NYHA class, exercise capacity, quality of life, ventricular function, heart failure hospitalizations and death (66, 67, 152, 153). Still, it has proven rather challenging to find the optimal response criteria (154) and no consensus definition of response/non-response has so far been reached (155). In theory, some patients may respond to CRT despite declining LV function and increasing HF symptoms, as they would have been even worse without. Given the costs and potential for complications with CRT implantation, however, the response has to be at a certain level to be considered clinically meaningful.

Most studies on CRT response prediction have used LV reverse remodeling as a surrogate endpoint defined as ≥10% or ≥15% reduction in LV end-systolic volume at 6 or 12 months follow-up. Reverse remodeling provides both a binary (response yes/no) and a continuous endpoint (degree of reverse remodeling) in every patient. Furthermore, it works well independent of pre-implantation heart failure severity and symptoms (73) and is related to HF hospitalizations and mortality (156-158). However, interobserver variability for LV end-systolic volume is considerable (90) and it may seem paradoxical that patients with ischemic etiology have least reverse remodeling, but most survival benefit (73). Recently, it was shown that improvement in GLS at 6 months follow-up was associated with improved long-term outcome independent of reverse remodeling, suggesting these parameters to be assessed together (159).

Improvement of symptoms and physical capacity is one of the primary goals in HF treatment and therefore frequently used as CRT response parameter. It has been shown, however, that such parameters do not necessarily correlate well with mortality (156). Furthermore, it may be challenging to identify improvement in the group of patients with only modest symptoms (NYHA class 2) prior to device implantation (73).

HF hospitalizations, heart transplantation and survival are highly clinically relevant and standard endpoints in randomized trials. Over the last years, such hard endpoints have also been used to define CRT response in observational studies (40, 81, 94), but have limitations when patients are not randomized. For example, patients who survive after CRT may do so due to favorable prognostic factors which are independent of CRT. Therefore, identifying survivors is not the same as identifying responders. Similarly, patients who die within the study period may have experienced positive CRT response as they would have died even before without CRT.

In total, every response parameter has its pros and cons which encourages the use of more than one response parameter. This is also why composite endpoints like the Packer clinical composite score (160) are relatively often used. Moreover, it highlights the need for randomized controlled trials.

Reasons for CRT non-response

There are fundamentally two reasons why CRT may not work. Either the therapy is applied in the wrong patient or it is not optimally delivered. Correct patient selection was the main topic in paper 3 and will be further discussed below. Reasons for suboptimal CRT delivery include scar in the region of the LV lead, lack of an optimal coronary vein, lead dislocation, suboptimal device settings and too low percentage biventricular pacing. Paper 3 would for sure have benefited by a detailed analysis of non-responders with regards to lead placement and percentage biventricular pacing. Potentially, such analysis would reveal that some of the

patients who were thought to become responders based on work difference and septal viability, became non-responders due to suboptimal pacing. The analysis, however, should not have been limited to non-responders as some responders probably would have responded even better with optimal CRT delivery.

Other mechanisms of CRT response

A limitation in paper 3 as well as many other studies on predictors of CRT response is the unilateral focus on intraventricular dyssynchrony and improvement in LV function. As previously explained, CRT have several modes of action including AV dyssynchrony, prevention of fatal bradyarrhytmias and improvement of mitral regurgitation. Although most people consider the effects on LV function most important, there is no clear consensus regarding the relative importance of the different mechanisms (69). As an example, data from MADIT-CRT showed that patients without LBBB QRS morphology only responded when there was AV conduction block, suggesting that the mode of action for response in these patients was improved filling (68). Furthermore, an experimental study from Boe et al. showed that in HF with narrow QRS, CRT improved LV filling, but the beneficial effect was counteracted by pacing-induced decrease in LV systolic function (161). There has also been attention toward the impact of ventricular interaction and, in particular, poor RV function has been suggested as an independent determinant of non-response (162). In a recent study from our group, it was found that LBBB leads to reduced workload on the RV free wall due to abnormal rightward septal motion. When septal function was normalized by CRT, RV workload was increased and, hence, a failing RV may not be able to compensate (163). In addition, the ability to recruit RV work was found to explain why LV pacing is as effective as biventricular pacing with regards to acute improvement in LV function in LBBB (151). In total, there is need for more clinical data on the impact of these mechanisms on CRT response.

What do we need from a CRT response marker?

Ideally, a marker of CRT response should be easy and cheap to measure, highly reproducible and feasible, and discriminate between responders and non-responders with high accuracy. QRS morphology and QRS duration are cheap and reproducible, but have limitations with regards to accuracy. In non-ischemic patients with typical LBBB configuration and very wide QRS, likelihood of response is high and in patients with QRS shorter than 130 ms positive response to CRT is unlikely and, instead, mortality may be increased (74). Additional evaluation may therefore be most important in patients with intermediate QRS duration (130-150 ms), non-LBBB configuration and/or ischemic cause of heart failure. This being said, a recent study found 35% non-responders also among patients with class 1 ESC guidelines indication for CRT (140).

For any given diagnostic test we extract sensitivity, specificity, positive predictive value and negative predictive value. The relative importance of these four numbers, however, depends on the setting. To improve current guidelines for CRT, it is essential to avoid implanting non-responders. Therefore, it may be argued that high specificity and negative predictive value are most important for a CRT response marker. A relevant clinical question is what the negative predictive value must be to refuse implantation of CRT. In this context, the risk for complications as well as the economical aspect should be considered.

Work and viability as a CRT response marker

In paper 3, we show that both work difference alone and combined with septal viability predicts CRT response with added value to current guidelines. Results are consistent both for LV reverse remodeling as primary endpoint, the combination of all-cause mortality and heart transplantation as secondary endpoint, and improvement in Packer clinical composite score. Feasibility and reproducibility was good for work difference, but a limitation is that the work method is somewhat more time-consuming compared with methods based on pure visual assessment. Feasibility for LGE-CMR is a limitation as a substantial number of patients both in the study and real-life have non-compatible pacemaker devices or poor kidney function making them unsuitable for contrast injection. Moreover, CMR is resource demanding and less widely available than echocardiography. Accuracy was reasonable for work difference alone, but may still be too low for clinical use. For the combined work and viability approach, however, both overall accuracy and specificity were good. The results were strengthened by the prospective and multi-centric study design as well as the inclusion of all-comers (poor image quality, atrial fibrillation, upgrades). Furthermore, work and viability was superior to alternative stand-alone approaches such as septal flash, apical rocking and systolic stretch index. In total, the combined approach of work and viability seems promising, but feasibility for LGE-CMR is a significant limitation. Access to CMR, however, may increase in the future and most modern pacemaker devices are CMR compatible. Still, the approach needs further testing in a randomized controlled trial before clinical use can be recommended.

Alternative approaches

As previously explained, a large number of echocardiographic indices have been proposed for CRT response prediction, but so far none of them have made their way into the guidelines (59). During the last years there has been a shift away from timing-based indices towards specific patterns of electromechanical dyssynchrony. Currently, septal flash, apical rocking and systolic stretch index are among the most promising methods and they all predict survival after CRT (81, 94). So, what are the advantages and disadvantages with these methods?

Septal flash and apical rocking are usually assessed visually and are in principle feasible in all patients with apical echocardiographic images. Furthermore, the method is quick and cheap, which is attractive in a busy echo lab. In typical cases it is easy to determine the presence of flash and rocking, but in our experience there are a relatively large number of cases with considerable doubt. It has been shown that augmentation of dyssynchrony by dobutamine stress echocardiography may help to categorize patients with borderline findings (164). However, as discussed above, the inconsistent definition of septal flash is also a challenge and may contribute to explain the substantial difference in reported prevalence even among patients with electrocardiographic LBBB configuration (94, 165). In addition, the intercenter variability for septal flash and apical rocking in paper 3 was considerable and substantially larger than for myocardial work. Readings, however, were performed without dedicated training and interobserver variability in expert centers has been substantially lower (94). Septal flash and apical rocking are qualitative parameters and, therefore, do not predict degree of response. This can be seen as a limitation since the expected degree of response may be clinically important, both in cases of limited resources and for patients with borderline indication. Predictive values of septal flash and apical rocking in paper 3 were similar to previous publications (94) and to work difference alone, but inferior to the combined approach of work and viability. It should be noted that readings used in the paper was performed in an expert center with extensive experience in the method.

Systolic stretch index is a strain-based method where contractile inefficiency is quantified as systolic stretch in the septum and LV posterolateral wall. Originally, it was calculated by radial strain (114), but more recently it has also been measured by longitudinal strain (81). In paper 2 and 3, we chose to calculate systolic stretch from longitudinal strain traces since small modifications of the region of interest may have large effects on radial strain values, leading to large interobserver variability (108). Additionally, in our experience, image quality is frequently insufficient for adequate tracking of radial strain. Using longitudinal strain, feasibility is similar as for LW-S work difference since both methods include septal and LV lateral wall strain. The systolic stretch index was developed based on computer simulations and it has been shown that it accounts for posterolateral scars (114), which was confirmed in paper 2. It is, however, more unclear whether it is able to identify septal scars. Increased stiffness and reduced contractility due to myocardial scar is likely to change the strain curves, but it may be hard to distinguish from pure electromechanical dyssynchrony in the individual patient with LV dyssynchrony. Accordingly, there was no significant difference in systolic stretch index between non-ischemic patients and patients with anteroseptal scars in paper 2. In paper 3, predictive values were borderline lower than for work difference alone, but substantially lower than the combined approach of work and viability.

Both septal flash, apical rocking, systolic stretch index and LW-S work difference assess the inefficient contraction pattern with loss of septal function and compensatory hyperfunction

of the LV lateral wall which is typical for LBBB and a key target for CRT. As stand-alone approaches they have different pros and cons, but the predictive values were relatively similar. It was found, however, that adding septal viability by LGE-CMR improved CRT response prediction considerably and this should therefore be considered independently of echocardiographic approach.

HF etiology and its relation to CRT response

In many patients, HF etiology is multifactorial. Coronary artery disease, valvular disease, hypertension, cardiotoxic treatment and genetic causes are important etiological factors. As previously explained, there is evolving evidence that LBBB can cause HF itself, but in most cases it is one of several factors. Assuming CRT can only partly correct the negative influence on LV function from LBBB, it may be useful to consider HF etiology in CRT candidates. For example, if a patient without any other detectable cardiac abnormality than LBBB eventually develops LV remodeling and HF, we can expect good response as the HF is solely caused by LBBB. In such patients, it may be that CRT should be implanted at an earlier stage than what is recommended by current guidelines (19, 20). On the other hand, when a patient with longstanding stable HF due to large post-infarct scar suddenly develops LBBB and worsened HF, we can only expect that CRT improves the component of HF which has evolved after onset LBBB.

LV dyssynchrony and CRT in patients without LBBB

As previously mentioned, LV dyssynchrony similar to what is seen in patients with classical LBBB, is often present in patients with RV pacing. Given the presence of septal flash or apical rocking, Stankovic et al. found that CRT response was similar for these patients as for LBBB patients (166). Another relevant situation is patients with combined RBBB and left anterior fascicle block. In such patients, there is early activation of the inferior wall and late activation of the anterior wall causing contraction pattern in the inferior wall similar to the septum in LBBB and contraction pattern in the anterior wall similar to the LV lateral wall in LBBB (167). Preliminary data indicates beneficial effect of CRT (167). Recently, it was also found that a number of patients with single-ventricle physiology after Fontan procedure showed typical strain pattern of LV dyssynchrony without LBBB (168). In total, it is likely that every scenario where regional delay of electrical activation leads to significant disturbance of LV contractile function can benefit from CRT. Importantly, however, mechanical dyssynchrony of non-electrical origin does not respond to CRT (74, 161).

Myocardial work in left bundle branch block

Myocardial work versus strain

In the present thesis, myocardial work is the most used parameter to quantify regional LV function. The main advantage of myocardial work over strain is the integration of afterload, which appears especially attractive when studying dyssynchrony.

As a large portion of septal shortening in LBBB occurs in early systole during low LVP, it represents only a small amount of work with minimal energy use. Therefore, normal values of septal shortening during dyssynchrony does not necessarily imply normal septal function. This was illustrated by the finding of low septal work in LBBB patients with peak septal shortening within the normal range (169). However, due to late-systolic stretch, septal end-systolic shortening is usually lower than peak septal shortening during dyssynchrony. As end-systolic values reflect net segmental shortening during systole, such values are likely to be more informative on septal performance during dyssynchrony than peak values. This is the reason why we reported segmental systolic shortening as end-systolic values.

The work method quantifies wasted energy as negative work and provides direct insight into myocardial metabolism (50). Septal systolic stretch means that the septum absorbs work performed by the LV free wall which is termed wasted since this work does not contribute to ejecting blood into the aorta. Such wasted energy may also be assessed by strain as for example with the systolic stretch index, but a pure strain parameter does not quantify energy to a similar extent as pressure is not taken into account.

Myocardial work for CRT response prediction

Myocardial work has previously been shown to predict CRT response both acutely in terms of stroke work (170) as well as long-term in terms of reverse remodeling and mortality (171-175). Compared to the study in paper 3, however, previous studies have been single center and either small and/or retrospective and have not included LGE-CMR as viability assessment. Most of them have focused on indices of global rather than regional work. Global values may be more robust, but less sensitive since the contractile inefficiency in LBBB primarily affects the septum and LV lateral wall.

Methodological considerations

Myocardial work

Myocardial work based on strain from echocardiography and brachial systolic cuff pressure has several limitations. Importantly, the use of pressure instead of force/wall stress and

strain instead of segment length does not provide a measure of work per se which is given in joules, but rather an index of myocardial work with the unit mmHg·%.

During dyssynchrony, wall thickness and radius of curvature differs between different segments within the left ventricle at a given time-point. As an example, in LBBB the early-systolic leftward septal motion leads to septal thickening and flattening when the LV lateral wall is still stretched. Such differences in regional wall stress is not taken into consideration when using pressure and may be important for regional work calculations. Furthermore, wall stress is substantially lower in a normal-sized ventricle compared with a ventricle that has undergone eccentric remodeling, which is the case with most CRT patients. In a small analysis of experimental LBBB data, however, there was good correlation between work calculated with pressure and wall stress (50). Moreover, in a study of myocardial ischemia, there were similar findings with pressure-segment length loops as with force-segment length loops (49). Although optimal, precise measurement of force is complicated. The previously mentioned law of Laplace is most frequently used and requires continuous measurement of both radius of curvature and wall thickness. These measurements are hard to obtain in daily clinical practice. In addition, estimating wall stress based on Laplace's principle assumes a symmetric geometry where wall thickness is considerably smaller than the cavity diameter. Hence, this calculation may be less accurate in the heart where these assumptions are not necessarily valid. It is important to emphasize that even though force would change the numeric work value compared with pressure, positive work would still be positive and negative work still negative. Therefore, the major differences between work in the septum and LV lateral wall in LBBB would still persist.

The methodology and built-in limitations of the non-invasive pressure curve was described in the methods section. As explained, timing of valvular events are important for the pressure estimate, but it has been shown that small offsets are not critical (50). Patients with atrial fibrillation, on the other hand, represent a challenge. In atrial fibrillation, LVP varies substantially from beat to beat, but this is hard to capture when measuring systolic blood pressure. In paper 3, we included a number of patients with atrial fibrillation and used the same average systolic pressure for all beats when calculating myocardial work. Although not likely to change the work difference substantially, this represents a fundamental limitation to the method.

Unlike segment length, strain is a measure of relative deformation. This is important when comparing hearts of different size (124). 2 mm shortening can for example give absolute strain values of 10% or 20% depending on whether end-diastolic length is 20 mm or 10 mm. This means that hearts of different sizes may perform the same amount of work with substantial differences in strain.

The work method was originally validated for speckle-tracking strain from echocardiography, but it was recently shown that feature-tracking strain derived from CMR may serve as a feasible alternative in patients with dyssynchrony (176). Compared to global strain, segmental strain is less reproducible and must be used with caution (177). Hence, the use of segmental strain represents a significant limitation to regional myocardial work analysis. Still, intercenter variability in paper 3 was relatively good, which may in part be due to the use of GE software which is probably the best for segmental strain analysis (178). Furthermore, segmental strain patterns which are especially important during dyssynchrony, seems to be more robust than peak and end-systolic values (177).

Importantly, myocardial work is currently not recommended for clinical use and should still be used as a research tool. Given technical progress, the use of three-dimensional echocardiography to obtain strain, valvular events, radius of curvature and wall thickness from a single view appears as an attractive future approach.

Experimental studies

The experimental studies enabled interventions with detailed hemodynamic assessment in a controlled setting. A major advantage is that every animal serves as its own control, thereby reducing the number of experiments needed. There are, however, some important limitations. First, the animals were heavily instrumented and under general anesthesia with cardiodepressive effects. In particular, every intervention directly to the heart leads to tissue injury of a certain extent and may affect results. Second, the use of an open-chest model has hemodynamic effects on cardiac physiology and especially LV filling. Third, LBBB induced by radiofrequency ablation does not necessarily reproduce what is found in a heterogeneous patient population. Fourth, there were several hours between baseline (normal electrical conduction) and LBBB recordings, which may in itself lead to deterioration of cardiac function. Fifth, acute experiments do not reproduce the effect of long-term dyssynchrony such as adverse remodeling.

Combining clinical and experimental studies

When an observed phenomenon in patients is reproduced by performing a specific intervention in an experimental model, the hypothesis of causal relationship is strongly supported. In paper 1 and 2, the clinical and experimental approaches complemented each other in this way.

Specific limitations

In paper 1, patients and controls were age-matched, and patients with known coronary artery disease were excluded. Anyhow, the study was small and it may well be that some LBBB patients had underlying subclinical heart disease which could contribute to explain the

observed differences in systolic function during increased afterload. Of note, three LBBB patients but no controls used beta blockers.

In paper 2, there was marked difference between experimental findings during septal ischemia and clinical findings in patients with septal scars. In the animals, septal rebound stretch increased with septal ischemia which is in line with previous findings from computer modeling studies (41). In patients with anteroseptal scars, septal rebound stretch was instead similar as in patients with non-ischemic cardiomyopathy. There may be several explanations for this finding. First, septal rebound stretch varies greatly among patients with LBBB and non-ischemic cardiomyopathy. It may therefore be that comparison of relatively small patient groups is unable to demonstrate a real difference. Second, although both acute ischemia and post-infarct scars lead to reduced contractility, ischemic myocardium is relatively elastic as compared to stiff scar tissue (102). Hence, rebound stretch may be reduced in scar patients due to stiff tissue which is harder to stretch. Third, many patients with anteroseptal scars showed apical dyskinesia. Hence, the apex may have absorbed displaced blood that would otherwise have caused stretch in the septum. Anyhow, this is a topic that needs further studies and the present findings must be interpreted with caution.

In paper 3, the use of reverse remodeling as a primary surrogate endpoint is a limitation, but is to certain degree compensated for by the inclusion of long-term data on mortality and heart transplantation as a secondary endpoint. The number of deaths and heart transplants, however, was relatively low leading to wide hazard ratio confidence intervals.

Ethical considerations

In the present work, many patients and a number of healthy controls have participated. Since the decision to implant CRT and the implantation procedure has been according to clinical routine, there has not been any extra risk associated with the procedure. However, patients have undergone uncomfortable interventions (extremity cuff inflation for afterload increase), they have spent extra time at the hospital and they have undergone additional imaging (compared to clinical routine). Although most patients have appreciated the additional investigations and follow-up, there has been a number of incidental findings with need for further follow-up, which has caused some concern among affected patients. This underscores the need for proper informed consent and approval from the Regional Ethical Committee.

There are important ethical issues with animal studies and particularly with dogs. Therefore, in our lab, such experiments are performed under very strict conditions. We adhere to the three Rs of animal research. This means **replacement** with a different species or avoid the use of animals at all if possible. In the present research, animals have been used as the

interventions could not be satisfactory performed with computer modeling and is unethical to do in humans. Dogs have specifically been used since interventions are only technically feasible in large animals and since dog is the species where induced LBBB resembles LBBB most closely to what is seen in humans (179). Furthermore, pigs do not tolerate the necessary surgical instrumentation and have a higher risk of premature death. Care is taken to **reduce** the number of animals to an absolute minimum by careful planning and combining as many interventions as possible. We typically collect data for several studies in each animal and data is frequently used retrospectively for new studies, effectively reducing the number of experiments. We also continuously **refine** our surgery and instrumentation techniques to reduce complication rates and improve data quality. Moreover, the experiments are acute with the animal in general anesthesia from the beginning until it is euthanized at the end, limiting potential pain and discomfort to a minimum. Experiments are also performed in a designated operating theater with certified personnel and approved by the National Animal Experimentation Board. Still, the use of dogs for research is controversial and as computer modeling continues to improve, it is likely that the use of animals will be further reduced.

10. CONCLUSION

The present thesis provides new insight into the effects of LV dyssynchrony on myocardial function and how this is related to CRT response. Our findings strongly support that septal dysfunction with asymmetric workload is the main mechanism for reduced LV function in LBBB and, therefore, the main target for CRT. Furthermore, it shows how septal dysfunction depends on contractility in the LV lateral wall and how it is aggravated by increased afterload.

Paper 1

LBBB patients are markedly sensitive to moderate acute elevations of afterload as compared to healthy controls. This exaggerated afterload response was attributed to increased septal dysfunction.

Paper 2

Septal dysfunction and, in particular septal rebound stretch, in LBBB is highly dependent on contractile function in the LV lateral wall. Therefore, LV lateral wall ischemia leads to marked improvement of septal function.

Paper 3

Marked work asymmetry with septal dysfunction and preserved LV lateral wall function identified a contractile reserve eligible for CRT. Given septal viability, work asymmetry predicted CRT response with high accuracy. When septal dysfunction was due to scar and could not be restored by CRT, response was unlikely.

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Paper 3

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CLINICAL RESEARCH
Imaging

Imaging predictors of response to cardiac resynchronization therapy: left ventricular work asymmetry by echocardiography and septal viability by cardiac magnetic resonance

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Aims Left ventricular (LV) failure in left bundle branch block is caused by loss of septal function and compensatory hyperfunction of the LV lateral wall (LW) which stimulates adverse remodelling. This study investigates if septal and LW function measured as myocardial work, alone and combined with assessment of septal viability, identifies responders to cardiac resynchronization therapy (CRT).

Methods and results In a prospective multicentre study of 200 CRT recipients, myocardial work was measured by pressure-strain analysis and viability by cardiac magnetic resonance (CMR) imaging ($n = 125$). CRT response was defined as ≥15% reduction in LV end-systolic volume after 6 months. Before CRT, septal work was markedly lower than LW work ($P < 0.0001$), and the difference was largest in CRT responders ($P < 0.001$). Work difference between septum and LW predicted CRT response with area under the curve (AUC) 0.77 (95% CI: 0.70–0.84) and was feasible in 98% of patients. In patients undergoing CMR, combining work difference and septal viability significantly increased AUC to 0.88 (95% CI: 0.81–0.95). This was superior to the predictive power of QRS morphology, QRS duration and the echocardiographic parameters septal flash, apical rocking, and systolic stretch index. Accuracy was similar for the subgroup of patients with QRS 120–150 ms as for the entire study group. Both work difference alone and work difference combined with septal viability predicted long-term survival without heart transplantation with hazard ratio 0.36 (95% CI: 0.18–0.74) and 0.21 (95% CI: 0.072–0.61), respectively.

Conclusion Assessment of myocardial work and septal viability identified CRT responders with high accuracy.

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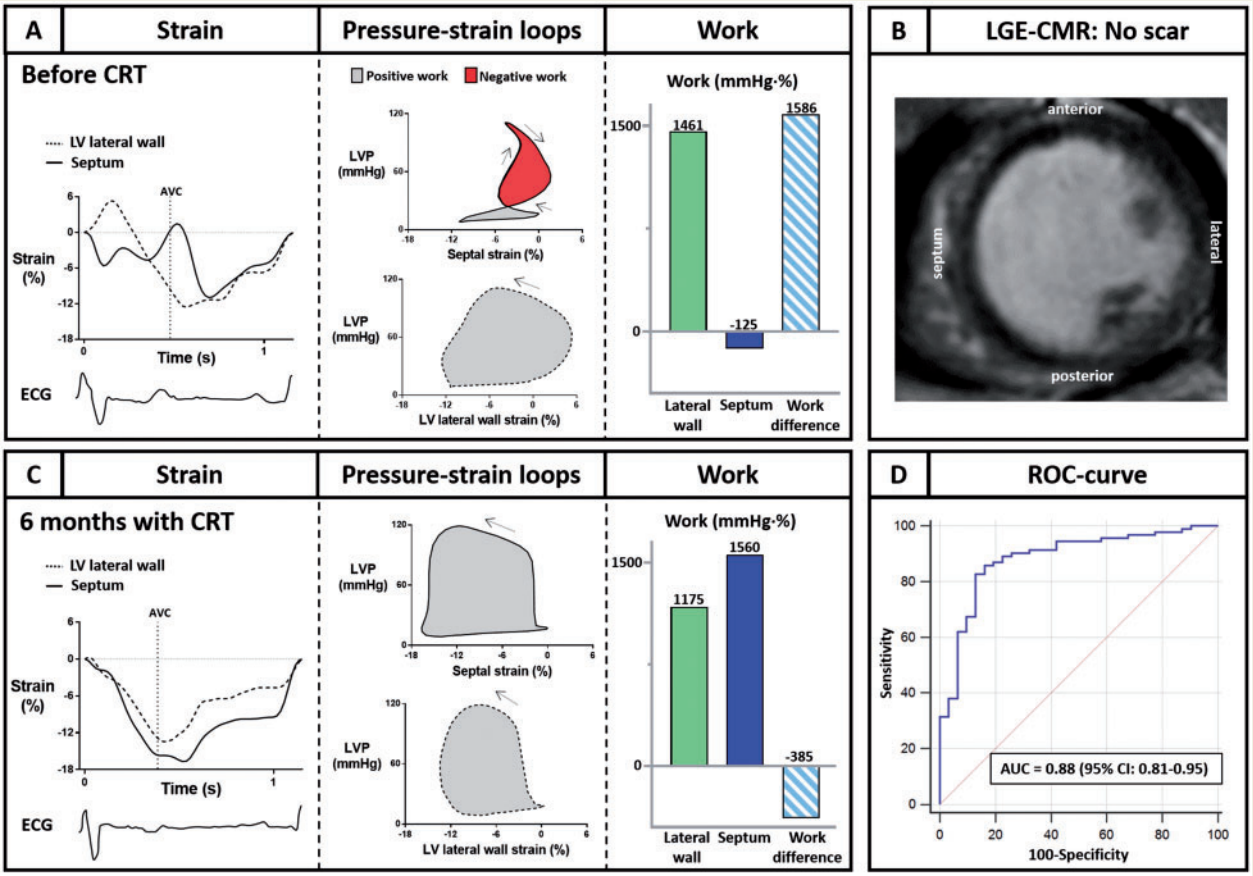
Graphical Abstract



Keywords Cardiac resynchronization therapy • Dyssynchrony • Heart failure • Left bundle branch block • Myocardial scar • Myocardial work

Introduction

Cardiac resynchronization therapy (CRT) is indicated in patients with symptomatic heart failure, reduced left ventricular (LV) ejection fraction (EF) and wide QRS in the electrocardiogram (ECG). A significant limitation of CRT is that 30–40% of patients show no improvement. In an effort to improve selection of patients for CRT, a number of echocardiographic measures of LV dyssynchrony have been tested, but none of these are proven to improve responder rate.[1] Therefore, current guidelines do not recommend echocardiographic measures of dyssynchrony or any other imaging tool when evaluating patients for CRT.[2]

In patients with left bundle branch block (LBBB), there is typically reduced contractile function of the interventricular septum which has a direct negative effect on global LV function, and there is compensatory hyperfunction of the LV lateral wall (LW) which stimulates adverse remodelling.[3] It was proposed by Prinzen *et al.*[3,4] that asymmetry in workload between the LW and septum could be a diagnostic indication for success of CRT. Furthermore, since restoration of septal function is important for recovery of LV function, we suggest septal viability as another determinant of response to electrical resynchronization. Therefore, in addition to work asymmetry between LW and septum, which reflects the disturbance of LV function in LBBB, we suggest assessment of septal viability to determine the potential for recovery of LV function with CRT.

The present study investigates the hypothesis that LW-to-septal work asymmetry and septal viability determines response to CRT. We used regional LV work rather than shortening indices to measure function since work quantifies the asymmetry in workload between LW and septum which is typical for LBBB. Myocardial work was assessed by a method innovated by the group of Smiseth, which uses a non-invasive estimate of LV pressure (LVP) in combination with myocardial strain by speckle-tracking echocardiography (STE).[5] Absolute rather than relative difference in work between LW and septum was used since septal work is often near zero in LBBB which results in large relative differences even when little work is done in the LW. Furthermore, the method takes into account reduced LW function due to LW scar, which is associated with non-response to

CRT.[6] To address the second part of the hypothesis, that viable septum is important for CRT response, we used late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR) imaging to assess myocardial scar.

A previous small feasibility study[5] and retrospective single-centre studies suggest that the work method may have a role in selection of patients for CRT.[7,8] The present study is the first clinical testing of the work method in a prospective multicentre study and investigates if myocardial work alone and combined with viability by LGE-CMR identifies responders to CRT with added value to current guidelines.

Methods

Study population

A total of 236 heart failure patients referred for CRT were prospectively included from Oslo University Hospital, Norway ($n = 101$), University Hospitals Leuven, Belgium ($n = 50$), Rennes University Hospital, France ($n = 71$), OLV Hospital Aalst, Belgium ($n = 11$), and Karolinska University Hospital, Sweden ($n = 3$) between August 2015 and November 2017. This constitutes about one-third of patients who received CRT in the main contributing centres during the study period. Inclusion criterion was indication for CRT according to 2013 European Society of Cardiology (ESC) guidelines.[9] Exclusion criteria contained recent myocardial infarction, recent cardiac surgery, and severe aortic stenosis. Thirty-six patients were excluded from the final analysis due to CRT not implanted ($n = 24$), study withdrawal ($n = 4$), lack of echocardiographic data ($n = 7$) or lead extraction due to endocarditis ($n = 1$). LGE-CMR was obtained in 125 of 200 remaining patients. Main reasons for not undergoing LGE-CMR were CMR non-compatible cardiac device ($n = 42$) and estimated glomerular filtration rate <45 mL/min/1.73m^2 ($n = 11$). For the remaining patients ($n = 22$), reasons included claustrophobia, intracranial metal implants, and logistical causes. Left bundle branch block was defined according to ESC guidelines.[9]

The study was approved by the respective Regional Ethics Committees and written informed consent was obtained from all study participants. The study was registered at clinicaltrials.gov (identifier NCT02525185).

Echocardiography and strain analysis

Echocardiography (Vivid E9 or E95 scanner, GE Vingmed Ultrasound AS, Horten, Norway) was performed before and 7 ± 1 months after CRT implantation. Recordings included two-dimensional (2D) grey-scale images from LV apical views for STE and timing of valvular events. Ventricular volumes and LVEF were obtained by biplane Simpson's method and blood pressure by the brachial cuff method at beginning of the examination.

Longitudinal strain was measured by STE and is presented as absolute values. In patients with atrial fibrillation, we analysed beats with approximately average heart rate. Frame rate was 66 ± 11/s.

Estimation of regional work

Myocardial work was calculated by a previously validated method.[5] The work index (mmHg·%) was calculated by multiplying rate of segmental shortening (strain rate) with instantaneous LVP. This resulted in a measure of instantaneous power, which was integrated over time to give work as a function of time in systole, defined as the time interval from mitral valve closure to mitral valve opening. Work performed during segmental shortening (i.e. counter-clockwise rotation of the pressure-strain loop) was defined as positive and work during segmental lengthening (i.e. clockwise rotation) as negative. Net myocardial work was calculated as the sum of positive (constructive) and negative (wasted) work for the given segment and globally as an average for all segments.

Regional work in the septum and LW was calculated as the average value of work from the respective basal and mid-ventricular segments in the apical four-chamber view. The absolute difference between net work in LW and septum (LW-S work difference) was used as a measure of asymmetry in workload. Myocardial work analysis was performed in Oslo by an observer blinded to volumetric measurements.

Alternative approaches

Septal flash[10] and apical rocking[11] were assessed visually in Leuven by two experienced readers. A visual reader interpretation of scar burden[12] was not performed. Systolic stretch index[13] was calculated from longitudinal strain traces as the sum of early-systolic stretch in the LW and septal systolic stretch.

Cardiac magnetic resonance and scar analysis

Prior to CRT implantation, patients were scanned with a 1.5 or 3.0 Tesla unit. LGE images were obtained after intravenous injection of either 0.15 or 0.20 mmol/kg gadoterate meglumine or 0.15 mmol/kg gadobenate dimeglumine. An experienced CMR radiologist made decision regarding presence of scar and, if positive, scar size was quantified semi-automatically in Segment software v2.0 R5270 from a stack of short-axis slices using a 17 segment model. We utilized the automatic algorithm EWA (expectation maximization, weighted intensity, a priori information).[14] Myocardial scar was reported regionally as percentage of total amount of tissue per wall and globally as percentage of total amount of tissue in the left ventricle. All scars were analysed and reported the same way independent of underlying aetiology.

Cardiac resynchronization therapy implantation

Patients underwent standard implantation of a biventricular pacing system. The implanting electrophysiologist had access to CMR images but was blinded to myocardial work data. Coronary venography was used to optimize placement of the LV lead in a lateral or posterolateral vein. The device was programmed in a conventional biventricular pacing mode and retested prior to hospital discharge.

Endpoints

Primary endpoint was reverse remodelling defined as at least 15% reduction in LV end-systolic volume (ESV) indexed to body surface area at 6 (7 ± 1) months follow-up. Reverse remodelling was chosen as it provides both a qualitative and quantitative endpoint, can be acquired in almost all patients, and is closely related to mortality.[15] To optimize precision, all volumes were measured independently in three different centres (Rennes, Leuven, and Oslo) and a majority decision was used in cases of disagreement on response. The pre-specified secondary endpoint was death at 12 months after CRT, but follow-up was extended and heart transplantation included to increase the number of events. Therefore, secondary endpoint was heart transplantation or death of any cause at 35 ± 11 (interquartile range 14) months after CRT implantation. As another measure of clinical response,[16] we assessed improvement in Packer clinical composite score[17] at 6 months.

Statistical analysis

All analyses involving myocardial scar were confined to the group of patients undergoing LGE-CMR. Values are presented as mean ±

Table 1 Baseline characteristics

	All patients ($n = 200$)	Responders ($n = 135$)	Non-responders ($n = 65$)	*P*-value
Age (years)	67 ± 11	68 ± 11	65 ± 11	0.041
Gender (%)				
Male	71	65	83	0.009
Weight (kg)	79 ± 16	75 ± 14	85 ± 17	<0.001
Heart failure aetiology (%)				
Non-ischaemic	65	76	43	<0.001
Ischaemic	35	24	57	<0.001
Medication (%)				
ACE-inhibitor/ARB	95	97	89	0.023
Beta-blocker	90	89	92	0.450
Aldosterone antagonists	41	39	46	0.304
Diuretics	71	69	77	0.263
Rhythm (%)				
Sinus	82	86	72	0.020
Atrial fibrillation	6	4	8	0.345
Paced	13	11	20	0.041
QRS configuration (%)				
LBBB	86	90	78	0.033
Non-LBBB	14	10	22	0.033
QRS duration (ms)	167 ± 21	168 ± 19	166 ± 24	0.497
Upgrades (%)	22	16	35	0.002
Systolic blood pressure (mmHg)	124 ± 21	126 ± 21	119 ± 20	0.020
Diastolic blood pressure (mmHg)	69 ± 11	70 ± 12	68 ± 10	0.318
NYHA functional class	2.4 ± 0.6	2.3 ± 0.6	2.5 ± 0.6	0.030
Mitral regurgitation (0–3)	1.2 ± 0.8	1.1 ± 0.8	1.4 ± 0.9	0.053

Continuous variables are given as mean ± standard deviation. *P*-value for comparison of responders vs. non-responders.
ACE-inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; LBBB, left bundle branch block; NYHA, New York Heart Association.

standard deviation or confidence intervals (CIs). Comparisons between two groups were performed using Student's *t*-test or chi-square test as appropriate. Univariate and multivariate linear regression analyses were used to identify predictors of reverse remodelling. Receiver operating characteristic (ROC) curves with area under the curve (AUC) values were used to determine discriminative ability. To combine assessment of two parameters, we used logistic regression to calculate a linear combination of the parameters, which was then used for ROC curves. The DeLong method or, when more appropriate, the Hanley and McNeil method (both MedCalc Software 2019) were used to compare ROC curves. Survival data are presented as hazard ratios (Cox regression) and Kaplan–Meier curves with log-rank test. As input, we used cut-off values from the primary endpoint analysis. Bland–Altman plot, Pearson correlation coefficient, intra-class correlation coefficient (ICC), and Cohen's kappa were used for reproducibility. If not otherwise stated, $P < 0.05$ was considered significant and IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp was used for analysis.

Reproducibility

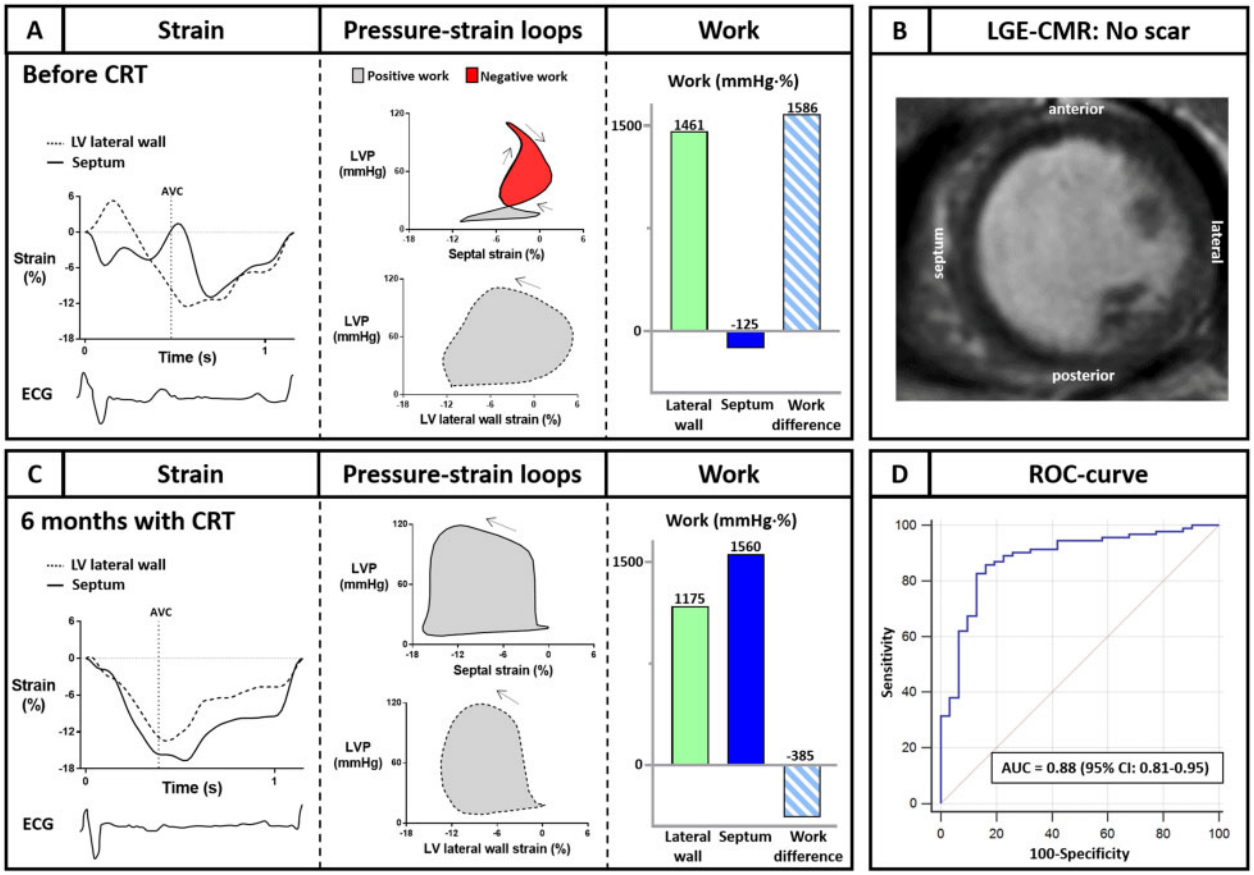
Excellent intra- and interobserver reproducibility for myocardial work has been reported previously.[5] Intercentre variability for myocardial work, septal flash, and apical rocking was studied in 38 randomly selected patients.

Results

At 6 months follow-up, there were three deaths, one heart transplantation and one LV assist device implantation, and these five patients were considered non-responders. The primary endpoint of ≥15% reduction in LV ESV index was achieved in 135 of 195 remaining patients, which gives 68% responder rate to CRT. Among responders, there were more females, patients in sinus rhythm and patients with non-ischaemic cardiomyopathy and a lower number of upgrades compared with non-responders (*Table 1*).

At follow-up, LVEF, GLS, and global work improved substantially in responders, while in non-responders there were no significant changes (*Figure 1A and B*, Supplementary material online, *Tables S1 and S2*).

The *Take home figure* is from a CRT responder with characteristic large lateral wall-to-septal work difference and viable septal myocardium. Prior to CRT, this patient has LV contraction pattern typical for LBBB with highly inefficient septal contractions due to substantial negative work, which was converted to positive work with CRT. The figure also illustrates how CRT reduced workload on the LW. Figure 2 shows a non-responder with essentially similar echocardiographic findings prior to CRT, but with significant septal scar indicating limited potential for septal



Take home figure Left ventricular work asymmetry combined with septal viability identifies cardiac resynchronization therapy responders. (*A*–*C*) The panels are from the same patient and illustrate how the lateral-to-septal work difference is used in combination with viability by LGE-CMR to identify cardiac resynchronization therapy responders. Before cardiac resynchronization therapy (*A*) there is dominantly negative septal work, as indicated by the red-coloured pressure-strain loop area, but compensatory increase in left ventricular lateral wall work, which gives a large lateral-to-septal work difference. Viable septum (*B*) indicates potential for recovery of septal function. After 6 months with cardiac resynchronization therapy (*C*), there is fine recovery of septal function. The highly inefficient septal contractions before cardiac resynchronization therapy are converted to positive work throughout systole. The improvement in septal function was accompanied by reduced workload on the lateral wall. (*D*) ROC curve displaying combined assessment of work difference and septal viability for cardiac resynchronization therapy response prediction (n = 123). AUC, area under curve; AVC, aortic valve closure; CI, confidence interval; LGE-CMR, late gadolinium enhancement cardiac magnetic resonance; LVP, left ventricular pressure; ROC, receiver operating characteristic.

recovery. Following CRT, there was only a moderate improvement of septal function.

Left ventricular work asymmetry

Large baseline LW-S work difference was associated with good CRT response both in the whole study population (*Figure 1B*) and when excluding patients with septal or LW scars. Univariate analysis revealed a direct relation between LW-S work difference and reverse remodelling ($r = 0.44$, $P < 0.0001$), where larger work difference was associated with more extensive reverse remodelling (*Figure 3*). Furthermore, in multivariate analysis, work difference together with heart failure aetiology (ischaemic or non-ischaemic) and QRS duration, but not QRS morphology (LBBB or non-LBBB), were independent predictors of reverse remodelling ($P < 0.0001$ for work difference) (*Table 2*). Work difference was somewhat larger in non-ischaemic as compared with ischaemic patients (1349 ± 702 vs. 955 ± 887 mmHg·%, $P < 0.001$).

AUC for LW-S work difference as predictor of CRT response in the entire study population was 0.77 (95% CI: 0.70–0.84) and was similar in the subgroup of patients with sinus rhythm and non-ischaemic aetiology. In comparison, AUC for QRS morphology (LBBB or non-LBBB) as predictor of CRT response was 0.56 (95% CI: 0.47–0.64) and for QRS duration 0.54 (95% CI: 0.45–0.63). Work difference ≥860 mmHg·% showed accuracy of 75% (95% CI: 68–81) for CRT response (*Figure 4A*, Supplementary material online, *Table S3*) and was a predictor of reduced risk for heart transplantation or death at long-term follow-up [hazard ratio 0.36 (95% CI: 0.18–0.74)] (*Figure 5A*). Furthermore, work difference was an independent predictor of improved Packer clinical composite score (Supplementary

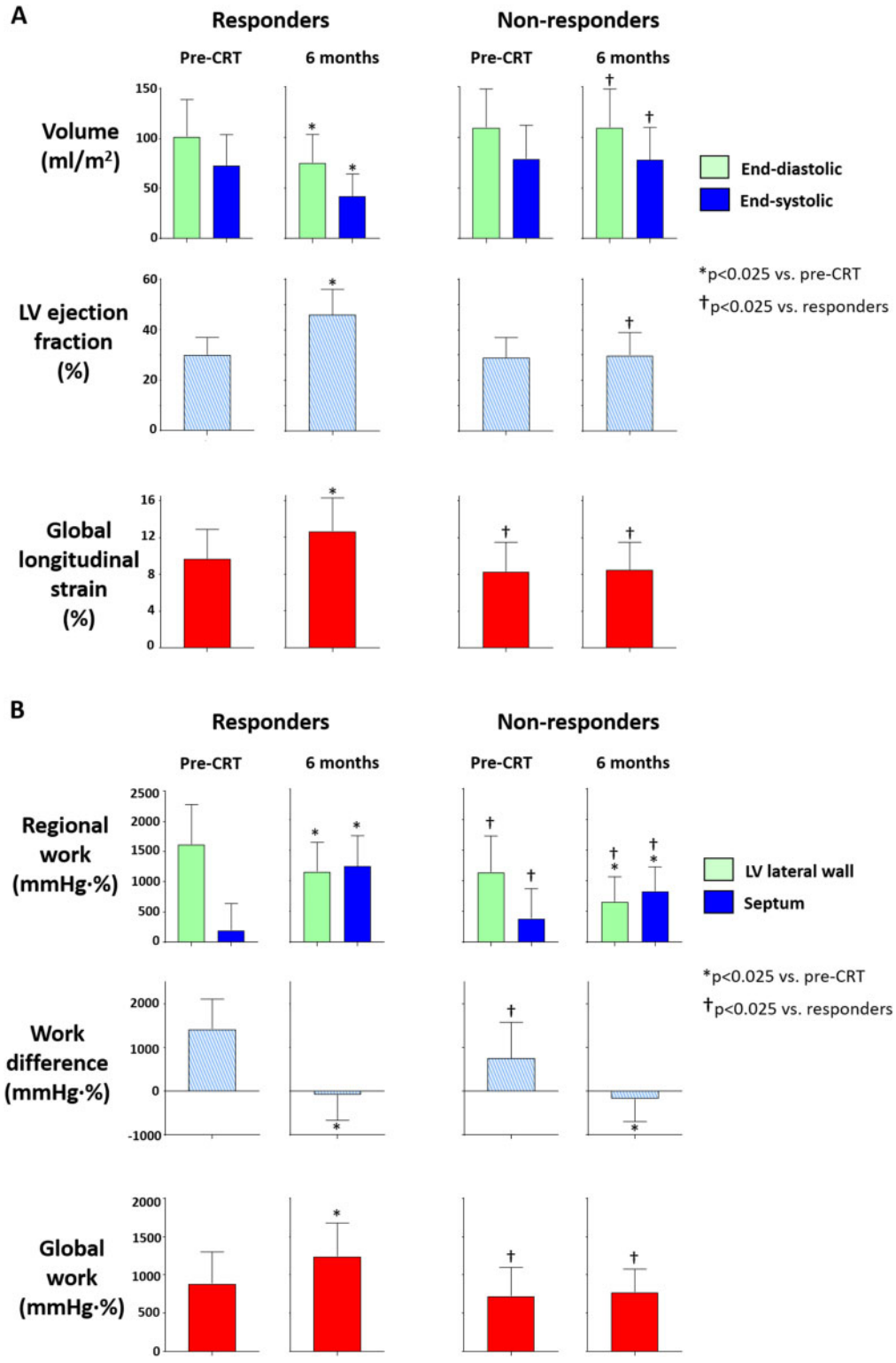


Figure 1 Left ventricular systolic function and work asymmetry. (*A*) Effect of cardiac resynchronization therapy on left ventricular volumes and function: Volumes and ejection fraction were similar in responders and non-responders before cardiac resynchronization therapy, but improved significantly only in responders. (*B*) Effects of cardiac resynchronization therapy on work: Before cardiac resynchronization therapy, responders have more work in the left ventricular lateral wall and less in the septum than non-responders (upper panels). This is reflected in a larger lateral-to-septal work difference (mid-panels). With cardiac resynchronization therapy, lateral wall work is reduced and septal work increased in both groups. Among responders, however, reduction in lateral wall work was far exceeded by increased septal work and explains why only responders showed improved global work (lower panels). One standard deviation indicated.

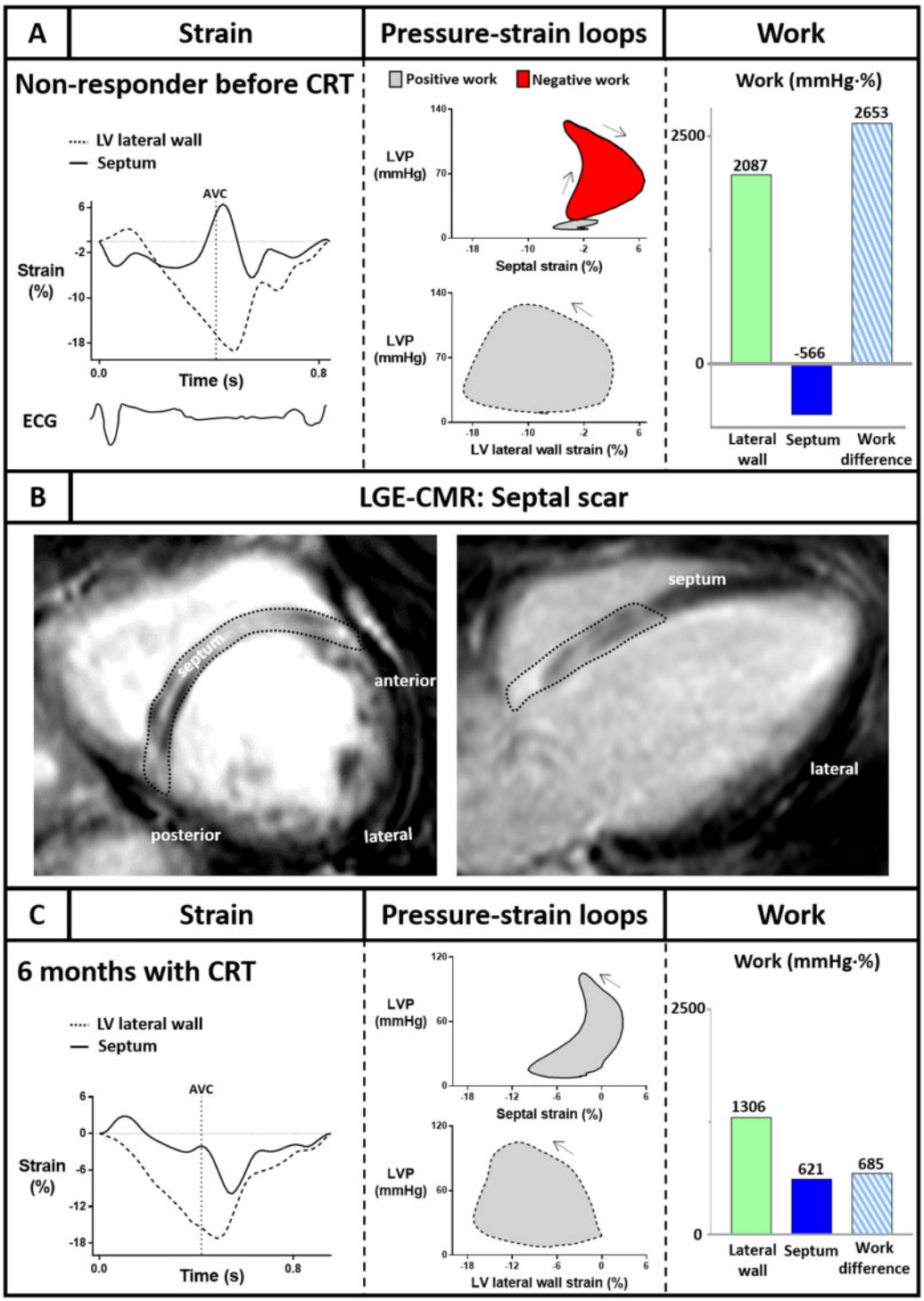


Figure 2 Septal scar identifies non-responder to cardiac resynchronization therapy. (*A*) Strain traces (left), pressure-strain loops (middle), and regional work (right) in a representative non-responder (with non-ischaemic cardiomyopathy) prior to cardiac resynchronization therapy. Similar to the patient in the *Take home figure*, there are highly inefficient septal contractions with predominantly negative work (red-coloured pressure-strain loop area), which leads to a large lateral-to-septal work difference. (*B*) LGE-CMR revealed extensive septal scar with limited potential for recovery of septal function with cardiac resynchronization therapy. (*C*) After 6 months with cardiac resynchronization therapy, there is only moderate recovery of septal function and, despite reduced workload on the left ventricular lateral wall, still significant lateral-to-septal work difference. AVC, aortic valve closure; LGE-CMR, late gadolinium enhancement cardiac magnetic resonance; LVP, left ventricular pressure.

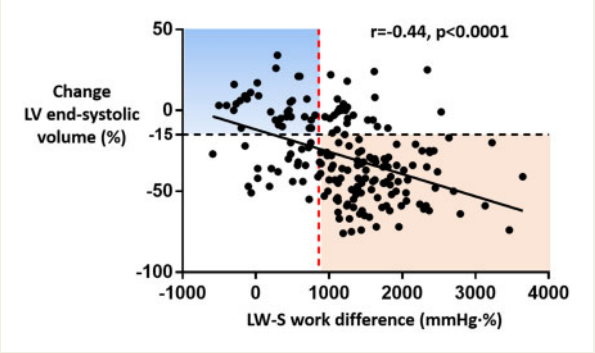


Figure 3 Regional work and reverse remodelling. Lateral-to-septal work difference correlates with degree of reverse remodelling following cardiac resynchronization therapy. The black-dotted line represents 15% reduction in left ventricular end-systolic volume index, whereas the red-dotted line represents the proposed cut-off value for work difference of 860 mmHg·%. LW-S, lateral-to-septal.

material online, *Table S4*). Assessment of work difference was feasible in 195 patients (98% feasibility).

Scar

LGE-CMR was performed in 125 patients, in whom scar was present in 61. Forty-six patients had some degree of scar in the anterior wall, 57 in the septum, 55 in the inferior wall, and 37 in the LW (Supplementary material online, *Table S5*). In univariate analysis, there was inverse correlation between total scar burden and reverse remodelling (r = -0.54, $P < 0.0001$).

Multivariate analysis including the percentage of anterior, septal, inferior, and lateral scar revealed that septal scar was a significant predictor of reverse remodelling (*Table 3*). Furthermore, the presence of any scar in the septum showed sensitivity of 81% (95% CI: 63–93) for non-response to CRT. AUC was 0.79 (95% CI: 0.69–0.89) (Supplementary material online, *Figure S2*).

Combining work and viability

There was inverse correlation between LW-S work difference and total scar burden (r = -0.43, $P < 0.0001$). In multivariate analysis including percentage of septal scar, LW-S work difference, QRS duration, and QRS morphology, only septal scar and work difference were significant predictors of reverse remodelling (both $P < 0.0002$) (*Table 4*). Furthermore, septal scar and work difference showed significant incremental value to a multivariate model for CRT response including QRS duration, heart failure aetiology and LV ESV index. In patients with septal scars, there was less improvement in septal work with CRT as compared to patients without scar ($P < 0.001$).

AUC for combined assessment of septal viability and LW-S work difference for CRT response prediction was 0.88 (95% CI: 0.81–0.95) (*Figure 4B*), which was significantly better than work difference alone ($P < 0.02$). The proposed cut-off value for the combined approach (*Figure 4B*) provided 86% sensitivity, 84% specificity, and 85% accuracy for CRT response and was a strong predictor of reduced risk for heart transplantation or death at long-term follow-up [hazard ratio 0.21 (95% CI: 0.072–0.61)] (Figure 5B). Combined assessment of work and viability significantly predicted improvement in Packer clinical composite score.

Table 2 Multivariate linear regression analysis with left ventricular end-systolic volume reduction as dependent variable

Regression variable	*B*	VIF	95% CI	*P*-value
Constant term	22.3			
QRS morphology	4.67	1.09	-4.65 to 13.99	0.324
QRS duration	-0.165	1.00	-0.317 to -0.014	0.033
Heart failure aetiology	-15.9	1.07	-22.6 to -9.3	<0.0001
LW-S work difference	-0.011	1.15	-0.015 to -0.007	<0.0001

$N = 190$. $R^2 = 0.29$.
CI, confidence interval; LW-S, lateral wall-to-septal; VIF, variance inflation factors.

Alternative approaches

Septal flash, apical rocking, and systolic stretch index predicted CRT response with AUC 0.74 (95% CI: 0.66–0.82), 0.75 (95% CI: 0.68–0.83), and 0.73 (95% CI: 0.66–0.81), respectively. There was no significant difference when comparing the ROC curve for LW-S work difference with septal flash and apical rocking. Compared with systolic stretch index, however, work difference was superior ($P < 0.05$). LW-S work difference combined with septal viability was superior to both septal flash, apical rocking and systolic stretch index (all $P < 0.025$).

Intermediate QRS duration

A total of 44 patients had QRS duration 120–150 ms (including three patients with QRS 120–129 ms), and 25 of these responded to CRT. In multivariate analysis ($n = 43$) including QRS duration and heart failure aetiology, LW-S work difference was the only significant predictor of reverse remodelling ($P < 0.02$). AUC for LW-S work difference was 0.82 (95% CI: 0.68–0.95).

For patients with QRS duration 120–150 ms undergoing LGE-CMR ($n = 27$), AUC for the combined assessment of septal viability and work difference was 0.91 (95% CI: 0.81–1.00).

Reproducibility

Bland–Altman and linear regression plots for intercentre variability of LW-S work difference are displayed in Supplementary material online, *Figure S3*. The ICC between the three centres was 0.89 (95% CI: 0.82–0.94) for septal work, 0.92 (95% CI: 0.88–0.96) for LW work, and 0.90 (95% CI: 0.84–0.94) for LW-S work difference, indicating good reproducibility. Furthermore, average intercentre agreement for work difference ≥860 mmHg·% was 89% (kappa range 0.65–0.85). Average intercentre agreement for presence of septal flash was 68% (kappa range 0.16–0.46) and for apical rocking 70% (kappa range 0.25–0.69).

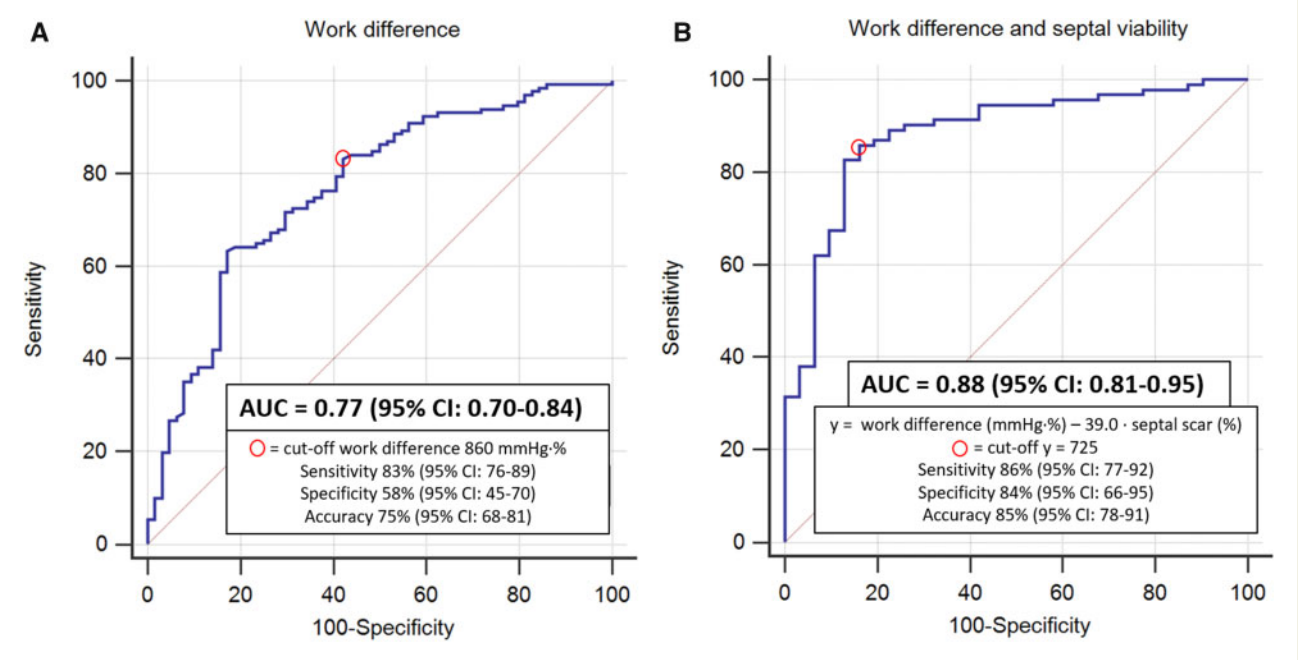


Figure 4 Work asymmetry and septal viability as predictors of cardiac resynchronization therapy response. (*A*) Receiver operating characteristic curve displaying lateral-to-septal work difference as predictor of cardiac resynchronization therapy response in the entire study population (n = 195). (*B*) Receiver operating characteristic curve displaying the combined assessment of lateral-to-septal work difference and septal viability as predictor of cardiac resynchronization therapy response (n = 123). AUC, area under curve; CI, confidence interval.

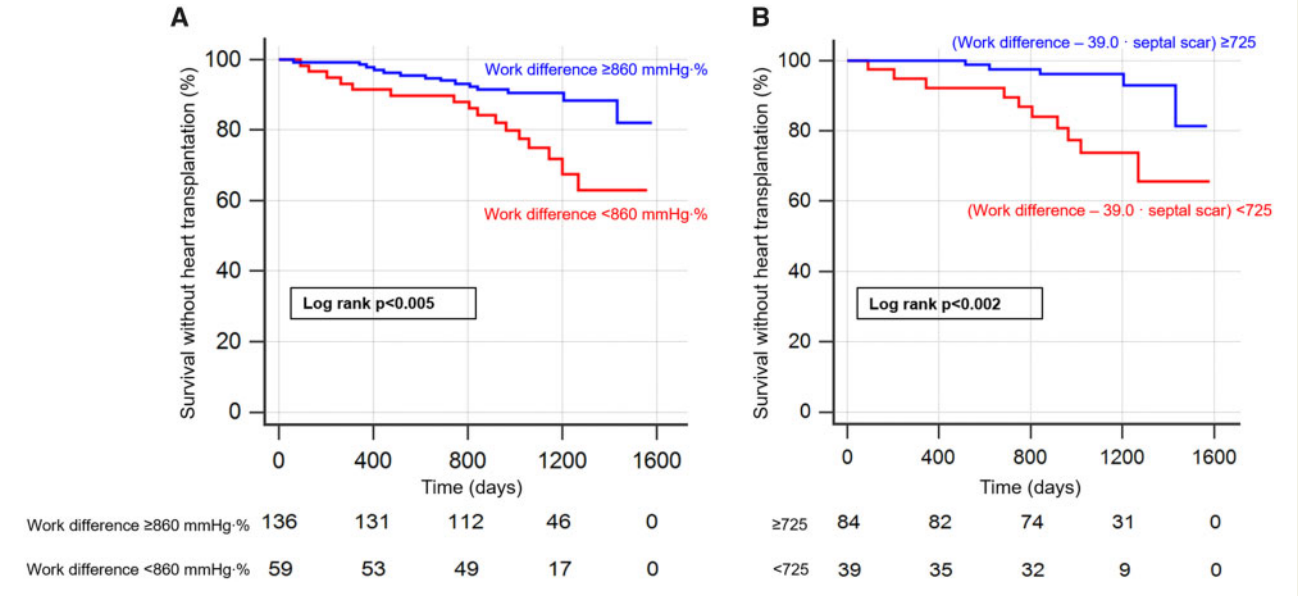


Figure 5 Association of work asymmetry and septal viability with long-term survival. (*A*) Kaplan–Meier curve stratified according to the proposed cut-off value for lateral-to-septal work difference. (*B*) Kaplan–Meier curve stratified according to the proposed cut-off value for lateral-to-septal work difference combined with septal viability.

Table 3 Multivariate linear regression analysis with left ventricular end-systolic volume reduction as dependent variable

Regression variable	B	VIF	95% CI	P-value
Constant term	-40.0			
Anterior wall scar	0.31	2.87	-0.05 to 0.66	0.088
Septal scar	0.42	3.17	0.04 to 0.80	0.029
Inferior wall scar	0.11	3.09	-0.22 to 0.45	0.503
Lateral wall scar	0.12	2.94	-0.21 to 0.45	0.479

$N = 122$. $R^2 = 0.33$. Regional scar was given as a continuous variable (%).
CI, confidence interval; VIF, variance inflation factors.

Table 4 Multivariate linear regression analysis with left ventricular end-systolic volume reduction as dependent variable

Regression variable	B	VIF	95% CI	P-value
Constant term	-1.15			
QRS morphology	8.70	1.13	-4.36 to 21.77	0.190
QRS duration	-0.15	1.07	-0.36 to 0.06	0.167
LW-S work difference	-0.009	1.13	-0.014 to -0.005	<0.0002
Septal scar	0.56	1.11	0.35 to 0.78	<0.0001

$N = 121$. $R^2 = 0.40$. Septal scar was given as a continuous variable (%).
CI, confidence interval; LW-S, lateral wall-to-septal; VIF, variance inflation factors.

Discussion

The present multicentre study extends previous smaller studies on myocardial work and presents the novel finding that quantification of myocardial work by echocardiography in combination with viability by LGE-CMR accurately identifies patients who will respond to CRT with reverse LV remodelling and predicts long-term survival after CRT. The patient population represented all-comers referred for CRT, including upgrades from other pacemaker devices, atrial fibrillation and patients with poor echocardiographic image quality. When septal work was markedly reduced relative to LW work and septal myocardium was viable, the responder rate was high. When there was reduced septal work and septal scar, and therefore limited potential for improvement of septal function, the patients were unlikely to respond. Importantly, precision was very good in the subgroup of patients with QRS duration 120–150 ms where recommendation for CRT is weaker or even absent according to current guidelines.[2]

Work and viability

The work method provides a more comprehensive measure of contractile function than just measuring tissue velocities or strain since it incorporates the effect of abnormal regional loading conditions during dyssynchrony. The work method also provides a measure of contractile efficiency since both the positive and negative (wasted) work are taken into account. A variable degree of systolic lengthening is common in LBBB and reflects inefficient contractions where the septum absorbs energy as a result of contractions in the LV free wall. The work method incorporates this important feature of dyssynchrony.

It is well-known that total myocardial scar burden and, in particular, scars located in the LV posterolateral wall are associated with non-response to CRT.[6] The latter is believed to be caused by inefficient pacing delivery. Furthermore, as shown in a recent study from our group, LW scar tends to normalize septal contraction pattern in hearts with LBBB.[18] This reflects that systolic stretch and contractile inefficiency of the septum in LBBB is caused by vigorous contractions in the LW. Therefore, when there is reduced LW function, there is less impairment of septal function and therefore less potential for improvement with CRT.

The observation in the present study that septal scar is a predictor of non-response to CRT is in keeping with a small study of 23 patients who received CRT.[19] In our study, the presence of septal scar alone identified non-responders with relatively high sensitivity. Since a contraction pattern with impaired septal function and preserved LW function may be seen also in patients with septal infarcts, viability imaging is essential.

Alternative approaches

Septal flash, apical rocking, and systolic stretch in the septum and LW are well-known features of mechanical dyssynchrony, which have been shown to predict response and mortality in observational studies of CRT recipients.[12,13] An advantage of septal flash and apical rocking is the quick visual assessment on echocardiographic B-mode images, but their qualitative nature is a limitation. In a previous retrospective study, septal flash and apical rocking were combined with visual echocardiographic assessment of scar burden to optimize response prediction, and results were promising.[12] However, as indicated in the intercentre variability analysis, visual assessment of septal flash and apical rocking showed considerable variability which could depend on degree of training of the observers. It is likely that reproducibility of these methods can be improved by standardization of the diagnostic criteria and dedicated training. The systolic stretch index is based on myocardial strain and provides a quantitative assessment of dyssynchrony, but does not incorporate afterload. Taking into account results from the present and previous studies, it is likely that these parameters and myocardial work reflect the same phenomenon; i.e. the abnormal and inefficient septal contraction pattern during LBBB.

Clinical implications

The combined approach of work and viability offers a new, precise, and relatively simple approach for selection of CRT candidates. Myocardial work difference can be measured by acquisition of the apical four-chamber view only which can be obtained in nearly all patients. The addition of CMR represents an additional cost, but a large number of centres already perform LGE-CMR as routine investigation prior to CRT to avoid placing the LV lead in a scar. If CMR is not available, myocardial work difference may be useful as a stand-alone tool. Due to higher number of non-responders, the proposed approach appears especially valuable for patients with ischaemic cardiomyopathy and/or intermediate QRS duration.

Limitations

In a substantial number of patients, LGE-CMR is not feasible due to previous pacemaker device. This will be easier with wider use of CMR compatible devices.

Data on LV lead position were not available and may have provided additional insights.

The use of non-invasive LVP based on average brachial cuff pressure represents a limitation in patients with atrial fibrillation where LVP varies substantially from beat to beat. Furthermore, using pressure as a substitute for force in the work calculation represents a limitation to the methodology. It has previously been demonstrated, however, that the impact of such limitation is minor in LBBB.[5]

The present study was observational with a limited number of patients and the primary endpoint was reverse remodelling. Hence, there is need for a larger randomized trial with primarily clinical endpoints before considering to change clinical practice.

Conclusions

In the present study, assessment of LV function as the LW-S work difference by echocardiography identified CRT responders with good accuracy. When combining work difference with septal viability by CMR, the accuracy to identify CRT responders was further improved. Thus, marked work asymmetry with reduced septal function, but preserved septal viability, identified a contractile reserve which was activated by CRT.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: O.A.S. is co-inventor, but since May 24, 2017 no financial relations to the patent 'Method for myocardial segment work analysis', which was used to calculate myocardial work. The other authors report no conflicts.

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Sammendrag

Venstre grenblokk betyr brudd i venstre hovedgren i hjertets spesialiserte ledningssystem slik at elektrisk aktivering av store deler av venstre ventrikkel istedenfor må skje gjennom vanlig myokard og derfor blir forsinket. Dette fører til usynkrone kontraksjoner (dyssynkroni) med negative effekter på venstre ventrikkels funksjon. Det typiske kontraksjonsmønsteret består av abnorm og dysfunksjonell bevegelse i det tidlig aktiverte interventrikulære septum med samtidig kompensatorisk hyperfunksjon i den sent aktiverte lateralveggen. Dette medfører en asymmetrisk arbeidsfordeling hvor septum gjør lite arbeid og lateralveggen mer enn normalt. Grenblokk kan oppstå både i pasienter med underliggende hjertesykdom og hos pasienter som er ellers friske. Tidligere var hovedoppfatningen at venstre grenblokk bestandig var en markør for underliggende hjertesykdom uavhengig av om denne var erkjent, og ikke en årsak til hjertesykdom i seg selv. Det har i senere år kommet flere bevis for at venstre grenblokk i seg selv kan føre til hjertesvikt, men de nøyaktige mekanismene og risikofaktorer for dette er ikke klarlagt. Videre er pasienter med venstre grenblokk, ejeksjonsfraksjon ≤35% og hjertesviktsymptomer kandidater for kardial resynkroniseringsterapi i henhold til gjeldende retningslinjer. Det er imidlertid en vedvarende utfordring at rundt en tredjedel av pasientene som får resynkroniseringsterapi ikke responderer på behandlingen.

I denne avhandlingen har vi studert venstre ventrikkels funksjon ved venstre grenblokk alene, og kombinert med iskemi, arr og økt afterload. Hensikten har vært å øke forståelsen av venstre grenblokks påvirkning på ventrikkelfunksjonen og spesielt mekanismene bak septal dysfunksjon. Ved hjelp av eksperimentelle dyreforsøk har vi kunnet måle den direkte effekten av iskemi og afterload, mens vi ved hjelp av kliniske studier har kunnet vise hvordan disse effektene gjør seg gjeldende hos pasienter. Videre har vi brukt innsikt i venstre grenblokks mekaniske påvirkning på hjertet til å predikere respons til kardial resynkroniseringsterapi i en prospektiv multisenterstudie. For å studere regional hjertefunksjon mer nøyaktig, har vi brukt et nytt ekkokardiografisk verktøy som beregner segmentalt arbeid i venstre ventrikkel, mens MR med gadolinium kontrast har blitt brukt til å vurdere arr.

Avhandlingen er basert på tre artikler. I den første har vi sett på effekten av økt afterload i hjerter med venstre grenblokk og normal ejeksjonsfraksjon. Hovedfunnet er at pasienter med venstre grenblokk er hypersensitive til akutt moderat stigning i blodtrykk da de reagerte med et langt mer uttalt fall i ejeksjonsfraksjon enn en alderssvarende kontrollgruppe. Hovedmekanismen for det uttalte fallet i ejeksjonsfraksjon så ut til være økende septal dysfunksjon, noe som ble bekreftet i den eksperimentelle delen av studien. Selv om studien var liten (11 personer i hver gruppe) og kun så på akutt stigning i blodtrykk, impliserer den at pasienter med grenblokk kan være mer sensitive også for kronisk trykkbelastning som ved arteriell hypertensjon eller aortastenose. Det er behov for videre studier for å avklare om

hypertensjon og aortastenose er spesielt disponerende for utvikling av hjertesvikt i venstre grenblokkspasienter og om dette eventuelt bør ha behandlingsmessige konsekvenser.

I artikkel nummer 2 studerte vi effekten av redusert septal- og lateralveggskontraktilitet på arbeidsfordelingen og spesielt septumfunksjonen i hjerter med venstre grenblokk. Hovedfunnet er at gode kontraksjoner i lateralveggen er en nødvendig forutsetning for septal dysfunksjon i venstre grenblokk. Ved å påføre lateralveggsiskemi i den eksperimentelle modellen, viste vi at den abnorme septumbevegelsen forsvant og at septumfunksjonen ble markant forbedret. Funnet ble bekreftet i pasienter med større lateralveggsarr og impliserer at de negative effektene av dyssynkroni er mindre uttalt i slike pasienter. Dette kan muligens bidra til å forklare at resynkroniseringsterapi fungerer dårligere i pasienter med lateralveggsarr.

I artikkel nummer 3 testet vi ut om asymmetrisk arbeidsfordeling i hjertet hos pasienter med venstre grenblokk kunne predikere respons til resynkroniseringsterapi. Vi utførte en prospektiv multisenterstudie med 200 pasienter fra fem ulike europeiske universitetssykehus. Primært endepunkt var respons til resynkroniseringsterapi definert som revers remodellering av venstre ventrikkel ved seks måneders oppfølging. Hovedhypotesen var at resynkroniseringsterapi kunne gjenopprette septal funksjon gitt at den reduserte septale funksjonen skyldes grenblokk og ikke arr. Vi brukte ekkokardiografi til å beregne arbeidet i septum og lateralveggen, og MR (n=125) til å påvise eventuelle septale arr. Hovedfunnet var at den asymmetriske fordelingen av arbeid mellom septum og lateralveggen predikerte CRT respons relativt godt med areal under kurven (AUC) 0.77, mens kombinasjonen av arbeid og septalt arr var signifikant bedre med en AUC på 0.88. Det kan spesielt nevnes at AUC-verdiene var tilsvarende i undergruppen av pasienter med intermediær QRS-varighet hvor indikasjonen for resynkroniseringsterapi er mer usikker i henhold til retningslinjer. Både arbeid alene og i kombinasjon med arr predikterte overlevelse uten hjertetransplantasjon.

Totalt sett viser funnene i denne avhandlingen at den asymmetriske arbeidsfordelingen i venstre ventrikkel med septal dysfunksjon og kompensatorisk hyperfunksjon i lateralveggen er en sentral mekanisme for den negative effekten av venstre grenblokk, og at utjevning av regionalt arbeid med gjenopprettelse av septumfunksjonen er et viktig mål for resynkroniseringsterapi. Dette kan forklare at pasienter med store septale og laterale arr har mindre gevinst av resynkroniseringsterapi. Videre indikerer funnene at grenblokkspasienter er sårbare for økning i blodtrykk som muligens kan bidra til å forklare hvorfor en del pasienter med grenblokk utvikler hjertesvikt.