Assessment of Mechanical Dyssynchrony in Cardiac Resynchronization Therapy

Probing the pathophysiology of activation delay-induced heart failure

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This thesis is based on the following papers:

PAPER I:
Risum N, Jons C, Olsen NT, Fritz-Hansen T, Bruun NE, Hojgaard MV, Valeur N, Kronborg MB, Kisslo J, Sogaard P. Simple regional strain pattern analysis to predict response to cardiac resynchronization therapy: rationale, initial results, and advantages.
Am Heart J. 2012 Apr;163(4):697-704.

PAPER II:
Risum N, Williams ES, Khouri MG, Jackson KP, Olsen NT, Jons C, Storm KS, Velazquez EJ, Kisslo J, Bruun NE, Sogaard P. Mechanical dyssynchrony evaluated by tissue Doppler cross-correlation analysis is associated with long-term survival in patients after cardiac resynchronization therapy.
Eur Heart J. 2013 Jan ;34(1):48-56.

PAPER III:
Risum N, Sogaard P, Jons C, Hofmann S, Fritz-Hansen T, Bruun NE, Velazquez EJ, Kisslo J, Olsen NT. Comparison of dyssynchrony parameters for VV-optimization in CRT patients.
Pacing Clin Electrophysiol 2013 Nov;36(11):1382-90.

BACKGROUND

CARDIAC RESYNCHRONIZATION THERAPY

The number of patients with chronic heart failure has increased throughout the last decades. Despite improved outcome based on pharmacological therapy primarily by inhibition of the renin-angiotensin-aldosterone system[1] and beta blockade[2] the prognosis remains poor. More recently, device-based therapies have emerged such as biventricular pacemakers which have caused a significant reduction in mortality in certain patient groups.

Approximately 30 % of heart failure patients have abnormalities in the myocardial conduction system which may lead to activation delays between the ventricular walls.[3-5] The resultant delay in contraction between walls is referred to as mechanical dyssynchrony. Dyssynchrony can be observed at different levels:[6] Interventricular dyssynchrony refers to the delayed contraction of one ventricle with respect to the other, whereas intraventricular dyssynchrony refers to a delayed contraction between LV walls usually of the lateral regions of the left ventricular chamber as compared to the interventricular septum. The latter has been shown to be the most important for outcome[7] and is the focus of the current thesis.

Biventricular pacing or Cardiac resynchronization therapy (CRT) was introduced in the early 1990's[8] and has proven to be one of the most important breakthroughs in treatment of heart failure. A CRT- device works by simultaneously pacing both the right and the left ventricle ´bypassing´ the intrinsic conduction system. In patients, where an activation delay causes heart failure, this may lead to re-coordination of left ventricular pump function.[9] Several prospective multicenter trials have demonstrated significant reduction in morbidity and mortality, left ventricular reverse remodeling, increased function and improved life quality from CRT.[10-16] For every 13 patients implanted with a CRT-device, one life is saved over a 3-year period when compared with medical therapy alone[17] and CRT is considered to be a cost-effective treatment.[18] However, more than one third of CRT-recipients do not respond and adverse outcome related to the procedure cannot be neglected with reported complication rates of 14 % and a perioperative death rate of 0.8 %.[17] Accordingly, CRT-candidates should be carefully selected and current criteria have to be refined to avoid too many nonresponders.

Until recently, patients were selected for CRT using three main criteria: 1) Left ventricular ejection fraction ≤ 35 %, 2) New York Heart Association (NYHA) functional class II-IV, and 3) QRS ≥ 120 ms (for NYHA class II > 150 ms). Substudies now suggest that mainly patients with LBBB ECG morphology and QRS duration > 150 ms respond[19] supporting the idea that current selection criteria for CRT may be suboptimal. The Danish Society of Cardiology no longer routinely recommends CRT for patients with RBBB or a combination of LBBB and QRS-duration between 120-150 (NYHA III-IV and LVEF ≤ 35%) but in selected cases, the decision to implant a CRT-device may be further supported by identification of mechanical dyssynchrony.[20] Others societies have come to similar conclusions with slight variations.[21]

Although response to CRT is multifactorial,[22] resynchronization of mechanical dyssynchrony is considered to be the primary mechanism behind response.[23] A wide QRS (>120 ms) is used as a surrogate marker of mechanical dyssynchrony. However, QRS-duration by itself is not a strong predictor of response to

CRT[24-28] and the correlation between QRS and mechanical dyssynchrony is poor.[6, 29-32] Pre-implant assessment of mechanical dyssynchrony by echocardiography may have additional value in selection of candidates for CRT.[33]

INTRAVENTRICULAR MECHANICAL DYSSYNCHRONY

Clinical detection and correction of mechanical dyssynchrony is dependent on an understanding of the abnormal physiology of the left ventricle induced by this disorder. For echo methods to be useful in selecting patients for CRT, ideally they must reflect some link between abnormal activation and mechanical contraction.[34] However, this link has not yet been firmly established.

In the normal heart, the LV walls are electrically activated almost synchronously with less than 40 ms delay between the septal and the opposing free wall.[35, 36] The uniform activation is due to rapid impulse conduction through the specialized conduction system of Purkinje fibres which divide into a right and a left bundle branch (LBB). The LBB further divides into a posterior and anterior fascicle which ensures a timely activation spread around the LV endocardium including uniform activation of the papillary muscles. The onset of segment shortening is likely closely related to timing of electrical activation.[37, 38] Accordingly, mechanical contraction of the LV walls in normal individuals occurs simultaneously.

Mechanical dyssynchrony is caused when electrical activation is delayed between walls. The hallmark conduction disease amenable to CRT is a complete LBB block (LBBB) where the left bundle is blocked and LV activation cannot take place via the normal pathways.[39] In this case, LV activation is dependent on electrical impulses traversing from the right side of the septal wall via the right bundle branch and the progression of activation towards the lateral free wall happening slowly by myocardial cell-to-cell conduction. [36] This condition can be mimicked by RV-pacing in animal models from which much of the initial knowledge regarding mechanical dyssynchrony was derived. [37, 38, 40] The early activated regions (septal wall) contracts first while the late activated walls (lateral free walls) are pre-stretched and contract late causing a dyssynchronous and inefficient LV pump action.[36] LV pump efficiency is reduced by 30%, primarily by reduction in stroke work and increase in oxygen consumption. [41] This causes progressive dilation of the LV chamber with increased wall stress. Dyssynchronous contraction of the papillary muscles leads to mitral regurgitation which may be further exacerbated by annulus dilatation as remodeling continues.

EVALUATION OF MECHANICAL DYSSYNCHRONY

Numerous methods have been proposed for evaluation of intraventricular mechanical dyssynchrony. Most commonly, this is performed by Tissue Doppler Imaging (TDI) [6, 24, 27-30, 42-45] or 2D-strain echocardiography (2DSE) [23, 46-49] using a time-to-peak approach. Time-to-peak differences in peak motion (displacement, velocities or strain) between walls above a certain cut-point is interpreted as dyssynchrony. Many publications have shown that mechanical dyssynchrony by this methodology, predicts LV remodeling, quality of life, functional class[27, 46, 48, 50-52] and reduces morbidity and mortality[23, 24, 43, 49, 53, 54] supporting a role for mechanical dyssynchrony assessment prior to CRT-implantation.

Time-to-peak measures initially included a clear promise that echocardiography could help in identifying patients with true mechanical dyssynchrony but problems have been encountered. PROSPECT55 was a multicenter study designed to answer whether pre-implant dyssynchrony evaluation, mostly TDI-indices, could predict response to CRT. The study failed to demonstrate a role for dyssynchrony evaluation and the variation in measurements was found to be unacceptably high. Unfortunately, the study was poorly executed somewhat undermining the conclusions. Lack of standardization in image acquisition and analyzes, the use of different vendors and software, and core laboratories with very different experience in dyssynchrony assessment were obvious limitations. [7] Nevertheless, this study had a large impact on clinical opinion and other studies have caused similar concerns for the high interobserver variability and the lack of predictive ability for some indices. [56-58]

Another objection to the time-to-peak approach is that it does not completely reflect the complex opposing wall motions caused by the underlying disordered pathophysiology of activation delay, likely necessary for CRT to be effective. [9, 50, 51, 59] Although a time-to-peak delay may reflect abnormal electrical activation, it can also represent heterogeneities of regional contractile function in the failing heart. [9] This distinction may be key if indices of mechanical dyssynchrony are to be implemented in clinical routine.

MECHANICAL DYSSYNCHRONY AND ACTIVATION DELAY-INDUCED HEART FAILURE

For the purpose of this thesis, the descriptive term activation delay-induced heart failure was used. This relates to the presumed primary target for CRT. Mechanical dyssynchrony is defined as disparity in regional contraction timing.[9] While this is observed in a number of disease states,[60, 61] surely not all mechanical dyssynchrony by this definition can be treated by CRT. Mechanical dyssynchrony induced by an activation delay is more easily appreciated as a target for CRT, while the role for resynchronization in patients without such delays is less clear.[9] However, it is acknowledged that other pathophysiologic mechanisms can be important for the development of heart failure in the presence of a significant activation delay. These mechanisms include concomitant disease states such as ischemic etiology, toxins, infiltrative processes, longstanding mechanical load from valvular or congenital causes, infections or a variety of inflammatory processes, as well as individual variations in genotype [62] and complex molecular processes.[63] Such alternate causes of heart failure will not be addressed in further detail in this thesis

While the status of current echocardiographic dyssynchrony analysis is controversial, the fact that a third of patients do not respond to CRT indicates that the need to improve the pre-implant assessment of mechanical dyssynchrony has not abated. Further study into the pathophysiology of what diagnostic criteria define activation delay-induced heart failure is needed.

OBJECTIVES

This thesis was based on the assumption that benefit from treatment with CRT requires a significant activation delay of the LV. It was hypothesized that echocardiographic methods for evaluation of mechanical dyssynchrony, reflective of this pathophysiologic change, could predict response to CRT. In addition, it was hypothesized that such methods would provide improved dyssynchrony analysis, as a diagnostic tool, compared to conventional time-to-peak methods.

A new semi-quantitative method based on assessment of strain-patterns was developed to characterize and separate patients with mechanical evidence of a significant LV activation delay and

those without. This method was then tested in prediction of response to CRT. In addition, a quantitative method for comparison of waveforms, cross-correlation analysis (XCA), with potential for separating those with and without activation delays was investigated. Mechanical dyssynchrony evaluated by XCA of TDI-derived data was tested for association with long-term outcome and for the purpose of device-programming.
The objectives were:
1) To identify strain patterns by 2DSE, reflective of a true LBBB, and investigate the prediction of response to CRT at six months. (Paper I)
2) To investigate the association of mechanical dyssynchrony assessed by XCA with long-term clinical outcome of CRT, and to study this method with respect to QRS-duration. (Paper II)
3) To compare XCA and time-to-peak methods for VV-optimization and study the effect of resynchronization in relation to hemodynamic performance. (Paper III)
4) To test if new methods for evaluation of mechanical dyssynchrony, thought to better reflect a significant LV activation delay, were superior compared to current time-to-peak indices. (Papers I, II and III)

METHODS

PAPER I - STUDY POPULATION

Sixty-seven consecutive patients were prospectively included between early 2009 and late 2010. Patients fulfilled the following indications for CRT; LVEF ≤ 35 %, QRS ≥ 120 ms and New York Heart Association (NYHA) functional class II or III. In addition, all patients had a LBBB by conventional criteria[64] as determined by the referring physician. All patients were treated in maximally tolerated dosages of beta-blockers, ACE-inhibitors/ angiotensin-II-inhibitors, spironolactone by the hospital out- patient heart failure clinic. Patients were excluded in case of atrial fibrillation, significant primary valve disease, acute coronary syndrome and/or revascularization inside three months of the baseline echocardiography and suboptimal biventricular pacing delivery (< 93 %). Finally, patients with very poor image quality incompatible with strain-analysis were excluded.
All patients had a full standard echocardiographic examination performed one day prior to CRT-implantation, at day one and six months after, including images optimized for TDI and speckle tracking analysis.

PAPER II – STUDY POPULATION

This study population comprised all patients from Gentofte University Hospital and Duke University Medical Center who received a TDI dyssynchrony study, prior to CRT implantation between August 2004 and April 2007. Seventy-one patients were identified from Duke (2004-2007) and 60 patients from Gentofte (2006-2007). Patients all fulfilled standard criteria for CRT at that time, LVEF ≤ 35 %, QRS > 120 ms and NYHA functional class II-IV at the time of implantation, despite optimal anti-congestive therapy. In none of the patients was the decision to implant a CRT-device affected by the dyssynchrony study.
Demographic data, clinical data, electrocardiography, echocardiography and routine laboratory work, including renal function, were obtained through chart reviews of cardiology and electrophysiology clinic notes. Patients were excluded if they had atrial fibrillation, acute coronary syndrome or revascularization within 3 months of the baseline echocardiography or if image quality did not allow TDI-analysis.
Vital status including implantation of left ventricular assist device (LVAD) or heart transplant (HTX) for all subjects was ascertained through chart reviews, the United States Social Security Death Index, and the Danish civil registration register, respectively, at the time of study analysis in November 2011.

PAPER III – STUDY POPULATION

Thirty-three consecutive patients referred for CRT-implantation were included. All patients fulfilled the following criteria at the time of implantation: LVEF ≤ 35%, LBBB, QRS ≥ 120 and NYHA functional class II or III, despite optimal medical treatment. Patients were excluded if they had significant primary valve disease, atrial fibrillation, or acute coronary syndrome or revascularization within three months of the baseline echocardiography.
A full standard echocardiographic examination was performed one day prior to CRT-implantation, at day one, and six months after CRT. At day one and after six months, all patients had AV-optimization performed at simultaneous pacing. Images were then acquired at different inter-ventricular pacing intervals for measurement of LVOT VTI and at six months this included images for 2D-strain and TDI-analysis for the purpose of dyssynchrony analysis. Images were acquired at six sequential pacing intervals; LV pre-activation by 60 ms (LV 60), 40 ms (LV 40), 20 ms (LV 20), simultaneous pacing (sim) and RV pre-activation by 20 ms (RV 20) and 40 ms (RV 40) in a random order.

ECHOCARDIOGRAPHY

All echocardiographic studies were performed on Vivid 7 (Papers I and II) or Vivid 9 (Papers I and III) ultrasound machines (GE Healthcare, Horten, Norway). All analysis was performed off-line blinded to outcome using EchoPac PC (version BT09 [paper I and II] or version BT11 [Paper III], GE Vingmed Ultrasound).

CONVENTIONAL ECHOCARDIOGRAPHY

Left ventricular volumes and LVEF were measured using the biplane Simpson method. The LVOT VTI was measured by pulsed-wave Doppler in the LVOT using a 2-mm sample volume positioned just proximal to the aortic valve, and data was obtained as an average of three measurements in three different heart beats during end-expiration.

SPECKLE TRACKING ANALYSIS AND DYSSYNCHRONY

Speckle tracking analysis was performed from 2D grey-scale loops (2DSE) in the three apical views (55-90 fps). The reference point was placed at the beginning of the QRS. Mitral valve closure (MVC), aortic valve opening (AVO) and aortic valve closure (AVC) were defined by tissue Doppler curved m-mode through the anterior mitral leaflet.[65] The endocardial border was traced in end-systole and the region of interest (ROI) was adjusted to exclude the pericardium. The quality of the tracings were automatically detected and confirmed visually. In case of poor tracking, the tracings were readjusted. Segments with persistent inadequate tracking were excluded from analysis.[66] Examples of speckle tracking analysis are shown in Figure 3.

Longitudinal strain

Longitudinal peak systolic strain was measured in all views between MVC and AVC for basal, midventricular, and apical segments and calculated into an averaged regional score for each wall (septal, lateral, inferior, anterior, posterior, and anterosep-

tal). Average global longitudinal strain (GLS) was calculated by averaging all segmental peak systolic strain values (correctly tracked). All strain analyses were performed blinded to outcome.

Dyssynchrony by time-to-peak strain

Dyssynchrony by the time-to-peak approach was assessed as the maximum opposing wall delay in time-to-peak strain among the three apical views from basal and midventricular segments (TPS-max) and a delay ≥130 ms was considered significant dyssynchrony (Paper I). [49] In addition, the standard deviation of time-to-peak in the 12 basal and midventricular segments (2DS-SD) was used (Paper III).[67]

Dyssynchrony by strain patterns

Based on previous descriptions of LBBB contraction patterns[37, 67, 68] and clinical observations, criteria for a strain-pattern thought to reflect a complete LBBB (a so-called 'classical' pattern) was defined by three components (Figure 1): (1) early contraction of at least one basal or midventricular segment in the septal or anteroseptal wall and early stretching in at least one basal or midventricular segment in the opposing wall, (2) the early peak contraction occurred in the first 70% of the systolic ejection phase, in case of double-peaks the first was chosen, and (3) the early stretching wall that showed peak contraction after AVC (holosystolic stretching segments do not fulfill the criteria).

The 70% cutoff for early contraction was based on preliminary observational data in 15 patients with ≤ LVEF 35% but no evidence of interventricular conduction delay from the ECG (QRS duration<120 ms). In none of these patients was early septal or antero-septal peak contraction in basal or midventricular segments present in the first 70 % of systolic ejection phase.

Patients who did not fulfill all three criteria were deemed as having a heterogeneous strain-pattern.

Reproducibility

Reproducibility of speckle tracking analysis was tested in 20 patients for GLS, TPSmax and 2DS-SD. For patterns, concordance was tested in 25 patients (Table 1).

TISSUE DOPPLER IMAGING AND DYSSYNCHRONY

Color TDI cine loops in each of the three standard apical views were acquired and optimized for sector width and depth to include the LV only. Color scale was adjusted to avoid aliasing. All TDI studies were performed at a frame rates between 95 and 150 fps.

Traces of myocardial velocities by TDI were obtained at the basal and mid-ventricular levels. TDI regions of interest (7x15 mm)[69] were adjusted for the most reproducible peak systolic velocities. AVO and AVC were determined as described above. Time-to-peak systolic velocity was measured from the beginning of the QRS complex, excluding the isovolumic periods.[27] An example of TDI analysis is shown in Figure 2, upper panel.

TDI-derived time-to-peak velocity dyssynchrony

Time-to-peak velocity between the septal and lateral wall (Ts-sl) was measured using the 4-chamber color TDI images from the beginning of the QRS complex, and the maximal time-to-peak difference between the basal segments of the septal and the lateral walls was calculated (Ts-sl). A predefined cutoff ≥65 was considered dyssynchrony.[70] (Paper I)

The opposing wall delay in time-to-peak velocities (OWD), was defined as the maximal time difference in peak velocity at basal and mid-segments in opposing walls for each view. Maximal OWD in one view ≥80 ms was considered dyssynchrony.[23] (Paper II). Finally, the Yu index was calculated as the 12-site time-to-peak velocity standard deviation (SD) in basal and mid-segments. Dyssynchrony by this index was defined as ≥32 ms. [23, 27] (Papers II and III)

CROSS-CORRELATION ANALYSIS

The TDI-derived velocity traces from basal segments were exported as text files (together with the electrocardiogram) into a customized spreadsheet (Microsoft Excel 2003; Microsoft Corp., Redmond, WA, USA) for XCA.51 The time period of interest between QRS onset and aortic valve closure was defined and the velocity data were converted to acceleration by temporal

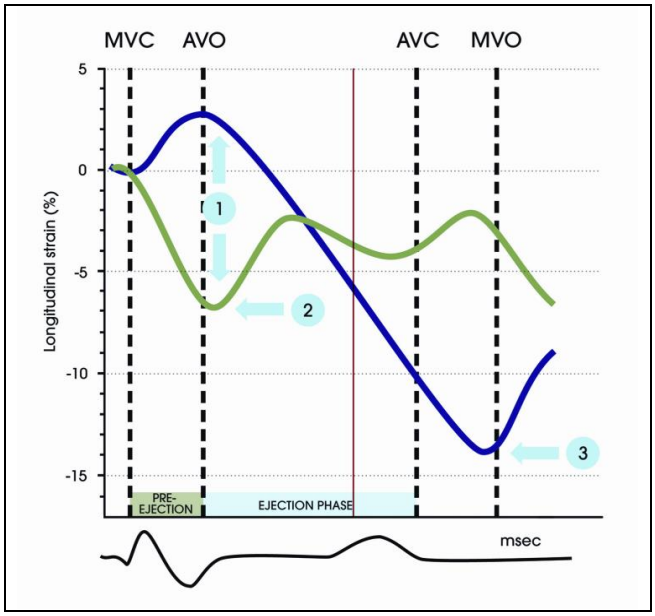


Figure 1. Definition of a classical pattern.

All of the following 3 criteria must be fulfilled: (1) Early contraction of at least 1 basal or midventricular segment in the septal or anteroseptal wall (green curve) and early stretching in at least 1 basal or midventricular segment in the opposing wall (dark blue curve). (2) Early peak contraction does not exceed 70% of the ejection phase (red vertical line). In case of double peaks, the first peak is considered. (3) The early stretching wall shows peak contraction after aortic valve closure (AVC). AVO, aortic valve opening; MVO, mitral valve opening.

differentiation. To reduce noise, three-point filtering was used. By the cross-correlation algorithm (in the spreadsheet), traces from opposing walls were compared according to the following formula:

$$XCC_d = \frac{\sum_i [(x_i - \bar{x}) \cdot (y_{i-d} - \bar{y})]}{\sqrt{\sum_i (x_i - \bar{x})^2} \sqrt{\sum_i (y_{i-d} - \bar{y})^2}}$$

where XCCd is the cross-correlation coefficient at time shift d, xi the acceleration trace from LV basal segment, yi the acceleration trace from opposing LV basal segment, and $\bar{x}$ and $\bar{y}$ represent the mean values.

The XCC is a measure of the degree of association between the acceleration traces, thus it investigates the similarity of the direction and magnitude of the acceleration in the two opposing walls. By time-shifting one acceleration trace relative to the other, frame-by frame in both directions, XCC is obtained for each time-shift and a spectrum created. The activation delay (AD) is the time shift necessary to obtain the best XCC. The analysis was performed in each of the three apical views to obtain the maximal absolute AD (AD-max) in each patient. Significant dyssynchrony by AD-max was defined as AD-max >35 ms as previously reported.[51]

Acceleration data were used because cross-correlation requires stationary means of the compared signals and translational or rotational motion of the heart can cause a drift in the velocity signal during systole which may affect the cross-correlation analysis. This can be compensated for by differentiating the velocity traces to obtain myocardial acceleration. Although acceleration traces are noisier, and additional filtering was necessary, cross-correlation analysis, and in particular the AD, is noise-insensitive because it is based on the overall patterns of many acceleration values. An example of XCA is shown in Figure 2, lower panel.

Reproducibility

Reproducibility of TDI and XCA was tested in 20 patients.

STATISTICS

Variables were tested for normal distribution using visual inspection of histogram plots and are presented as either mean ± SD or median with interquartile range. A paired sample t-test or Wilcoxon signed rank was used to compare measurements of paired groups. For unpaired groups a two-sample t-test or Mann-Whitney test were used as appropriate. Categorical variables were tested for differences using $\chi 2$ statistics or Fischer´s exact test.

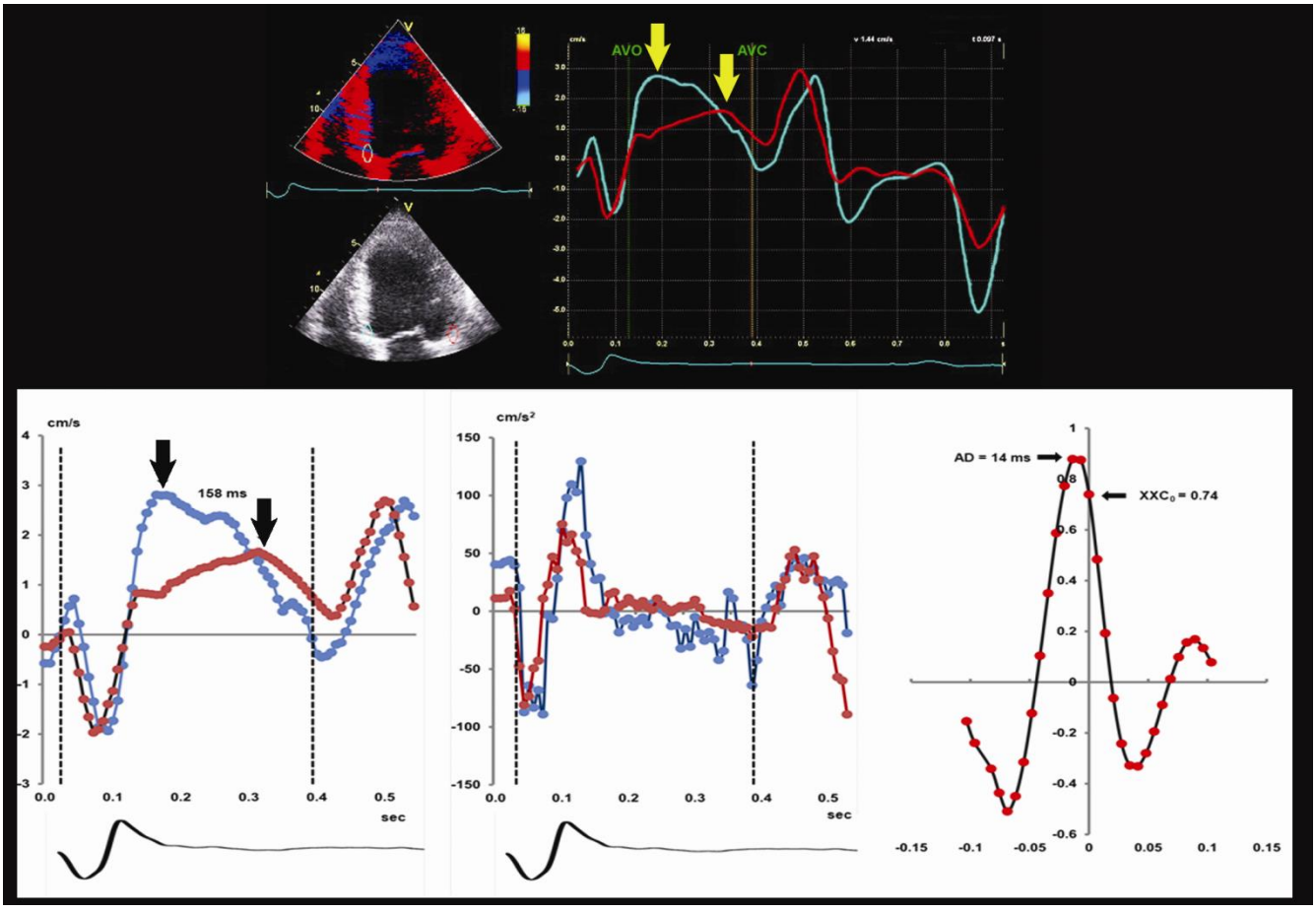


Figure 2. From tissue velocity traces to cross-correlation analysis of acceleration.

Lower panel: Same patient. Differentiation of tissue Doppler velocity traces (left column) generates the acceleration traces (middle column). Cross-correlation coefficient spectrum (right column) is calculated from the systolic periods (between dashed lines) of the acceleration curves.

This example shows a 68-year-old man, who did not respond to cardiac resynchronization therapy. The patient had ischemic dilated cardiomyopathy, LBBB, New York Heart Association class III and left ventricular ejection fraction of 28%. Time-to-peak velocity analysis showed a significantly delayed lateral wall (158 ms between vertical arrows). In contrast, acceleration analysis yielded a high XXC0 (0.74) and a low activation delay of 14 ms (horizontal arrows). Thus, the patient did not have significant dyssynchrony.

and strain values over time were investigated by a linear mixed model. A random effect for the individual patient was added to the model, and the model run with only the variable for LV dyssynchrony/strain difference. The ability of dyssynchrony indices to categorize subjects as responders or nonresponders was compared using two log-likelihood statistics in a multivariate logistic regression model including etiology and QRS ≥ 150 ms. Paper II: Follow-up was truncated at 4 years for survival analysis. The cumulative probability of the endpoint was illustrated by the Kaplan–Meier method with significance testing using log-rank statistics. Predictors of event-free survival after CRT device implantation were evaluated in Cox's proportional hazards models. Covariates previously shown to predict mortality from heart failure were included. The independent association between

Table 1. Reproducibility of speckle tracking analysis

Measure	Number of patients	Mean difference (SD)	Coefficient of variation, %	Observer Agreement
GLS, %	20	0.2(1.0)	6.8	-
TPSmax, ms (paper II)	20	1.3(16.3)	13.5	-
2DS-SD, ms (paper III)	20	-0.7(5.5)	11.3	-
Pattern (intra-)	25	-	-	25/25
Pattern (inter-)	25	-	-	24/25

Coefficient of variation is calculated as SD of difference between repeated measurements divided by the mean value.

Table 2. Reproducibility of TDI-derived dyssynchrony indices

Measure	Number of patients	Mean difference (SD)	Coefficient of variation, %
Yu-index (Paper II), ms	20	1.1(3.7)	6.2
Yu-index (Paper III), ms	20	-0.1(5.5)	11.5
OWD (Paper II), ms	20	2.0(4.0)	6.4
AD-max (Paper II), ms	20	-2.0(2.2)	4.0
AD-max (Paper III), ms	20	-1.9(3.1)	6.3
Yu-index (Paper II), ms	20	1.1(3.7)	6.2

Coefficient of Variation is calculated as SD of difference between repeated measurements divided by the mean value.

outcome and each dyssynchrony index was tested in a multivariable model after backward selection from candidate variables ($p < 0.1$ in univariate analysis). For comparison between indices, the strength of association for each dyssynchrony index was compared using 2 log-likelihood statistics. Receiver operating characteristic (ROC) curve analysis was performed for each dyssynchrony index with the use of a nonparametric estimate of the area under the curve (AUC) and c-statistics with 95% confidence interval (CI) were performed for each multivariable model. [71] The ability of AD-max > 35 ms to reclassify patient risk when added to a multivariable model with either Yu index ≥ 32 ms or OWD ≥ 80 ms was evaluated by assessment of the net reclassification improvement (NRI). [72] Patients were initially classified as at low or high risk of an event if their predicted risk was <10 or ≥10%, respectively.[15] Patients were then reclassified (or unchanged) into a different category with the addition of AD-max > 35 ms.

Paper III: Agreement between optimization methods was evaluated by weighted (quadratic) kappa statistics, with $0.6 < \kappa < 0.8$ representing good agreement.

A p–value < 0.05 was considered statistically significant. All statistical analyses were performed using SAS for Windows version 9.1.3 (SAS institute, Cary NC, USA).

MAIN RESULTS

RESULTS - PAPER I

Of 67 included patients, one was excluded at six months because of suboptimal pace delivery of 82%. Mean follow-up was 6.7 ± 1.3 months and mean biventricular pacing was 97 % ± 2%. Forty-three patients (65%) were responders.

Strain-patterns in prediction of response

The type of contraction pattern identified was highly predictive of response to CRT. Forty-three patients had a classical pattern, of these 41 were responders. In contrast, a heterogeneous pattern was identified in 23 patients of whom only 2 responded to CRT. Thus, the presence of a classical pattern was 95% sensitive and 91% specific for response. Furthermore, a classical strain pattern significantly added to clinical predictors nonischemic etiology, p = .04, and QRS >150 ms, p = .008. One particular type of a classical pattern with early terminated isovolumic contraction,(i.e. septal flash) showed the highest potential for response. Eighteen of 25 (72%) patients with a septal flash had an improvement in LVESV of > 30%.

Time-to-peak indices performed less well compared to evaluating patterns ($p < 0.001$, both). Sensitivities and specificities were 95% and 16% for TPSmax and 55% and 68%, for Ts-sl, respectively. Representative examples of a classical and a heterogeneous pattern, respectively, and the response to CRT at day one and six months are shown in Figure 3.

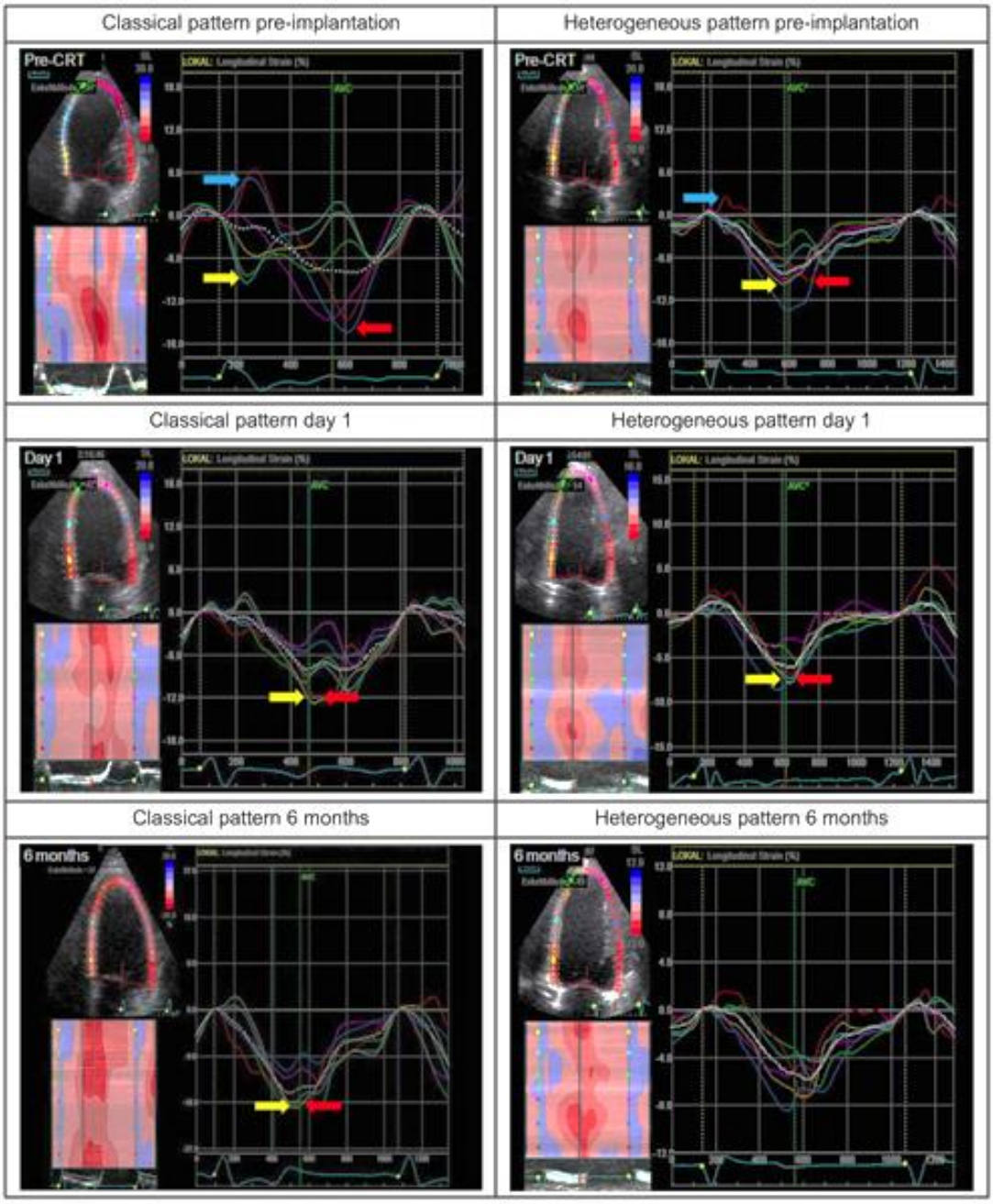
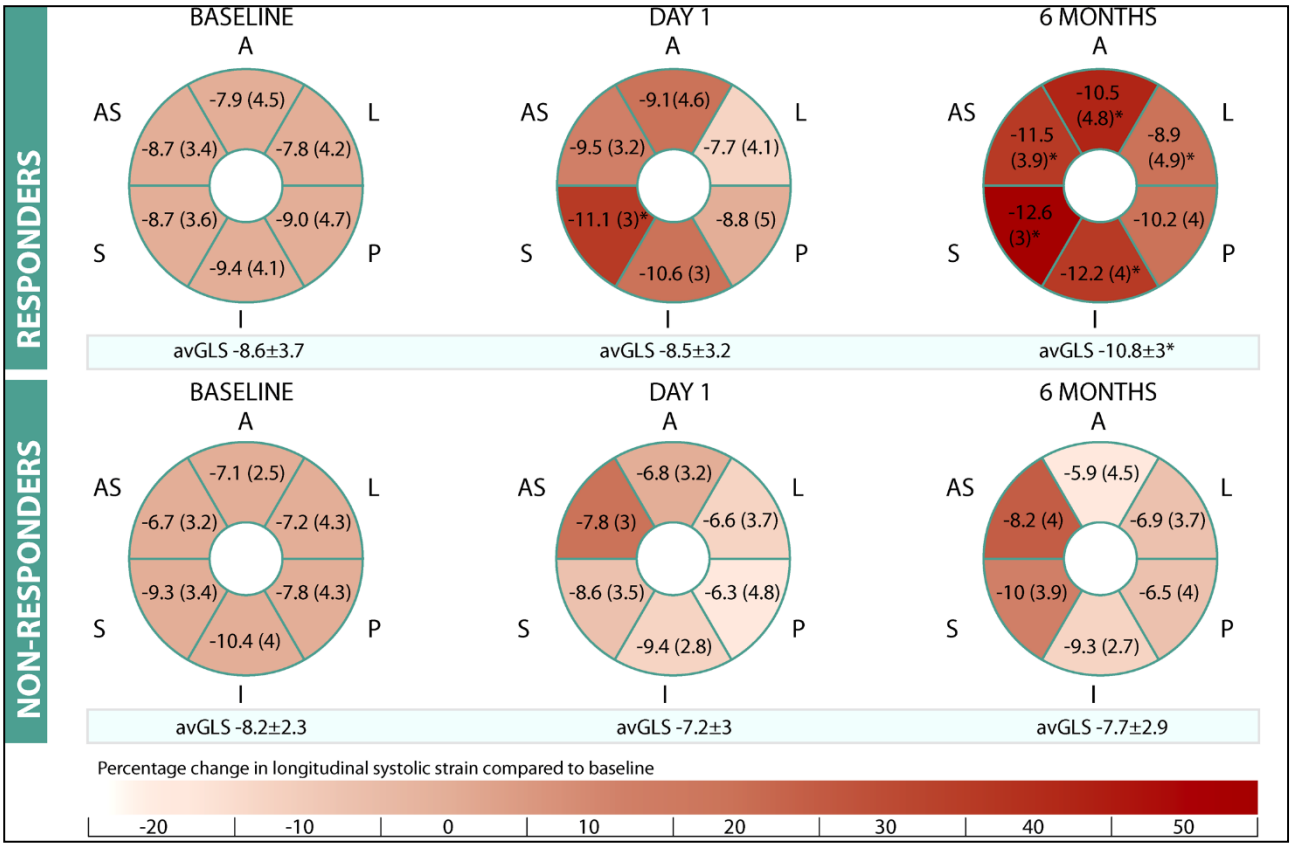


Figure 3. Changes in contraction patterns from CRT. *Right column, Classical pattern. Top: Classical pattern of LV dyssynchrony in the 4-ch view pre-CRT. The early activated septal wall shows early peak contraction (yellow arrow), while the late activated lateral wall is pre-stretched (blue arrow) followed by late peak contraction after aortic valve closure (AVC) (red arrow). Mid: At day 1 after CRT, peak contraction is aligned with improved systolic septal strain (yellow arrow), while lateral strain is decreased (red arrow). Bottom: At 6 months after CRT, peak contraction is aligned with global improvements in strain values (yellow and red arrows).Left column, Heterogeneous pattern: Top: Pre-CRT heterogeneous pattern in the 4-ch view. The basal segment in the lateral wall exhibits pre-stretching (blue arrow) followed by late peak contraction (red arrow). However, the opposing septal wall shows a normally timed peak contraction at AVC (yellow arrow). Mid: At day 1 after CRT peak contraction is aligned but no improvements in regional strain are observed. Left column bottom 6 months after CRT. Peak contraction is aligned but no improvements in strain are observed. Bottom: At 6 months after CRT, peak contraction is aligned but no global improvements are observed.*



Figur 4 Summary of regional strains.

*Bull's-eye plots presenting LV longitudinal peak systolic strain values in responders and nonresponders at baseline, day 1, and 6 months evaluated in each of the 6 LV walls. Values are measured for the basal, midventricular, and apical segments and calculated into an averaged regional score for each wall. Average global longitudinal strain (AvGLS) was calculated by averaging all segmental peak systolic strain values. Color intensity coding refers to the percentage change in longitudinal systolic strain compared with baseline values. Values represent mean (±SD) *p < 0.05 versus baseline. A, anterior wall; L, lateral wall; P, posterior wall; I, inferior wall; S, septum; AS, anteroseptal wall;*

Mechanisms behind response to CRT evaluated by strain

Left ventricular strain values at baseline, and changes at day one, and six months after CRT for responders and non-responders are shown in Figure 4. Characteristic differences between responders and non-responders were observed during the course of treatment. Short-term CRT caused a highly significant improvement in septal wall strain in the responder group ($p < 0.001$), but not in non-responders ($p = 0.22$) and no significant changes were observed at day one in any other walls. In 38/41 responders (93%) with a classical pattern, the septal region was the earliest contracting region. In responders, all LV walls improved in systolic strain at six months when compared with baseline ($p > 0.05$, all), while no improvements were observed in nonresponders.

With regards to changes in time-to-peak dyssynchrony both responders and nonresponders showed a significantly reduced TPS-max at day one ($p > 0.05$, both groups), which was sustained during treatment with no significant differences between groups (responders: from 253 ± 106 ms to 148 ± 71 ms to 140 ± 53 ms; nonresponders: 195 ± 87 ms to 136 ± 93 ms to 127 ± 53 ms; $p > 0.05$, all).

Assessment of AD-max was possible in 121 patients (92%) while evaluation of the Yu index and OWD was possible in 116 patients (89%).

RESULTS - PAPER II

Mechanical dyssynchrony and association with long-term outcome One hundred and seventeen (97%) patients had maximum 4-year follow-up. During the follow-up period, 31 patients (26%) died, one patient (0.8%) received an LVAD and none of the patients had a heart transplant (HTX). Dyssynchrony by AD-max was associated with a significantly longer event-free survival compared with patients without dyssynchrony ($p = 0.001$) as shown in Figure 5. Yu index and OWD only showed borderline significant association with outcome ($p = 0.09$ and 0.06, respectively). Covariates LBBB morphology, non-ischemic etiology, and QRS duration >150 ms were all significantly associated with outcome (Table 3). In multivariate analysis (Table 3), dyssynchrony by AD-max was independently associated with event-free survival [hazard ratio (HR) 0.35 (95% CI 0.16–0.77), $p = 0.01$], while OWD and Yu-index were not.

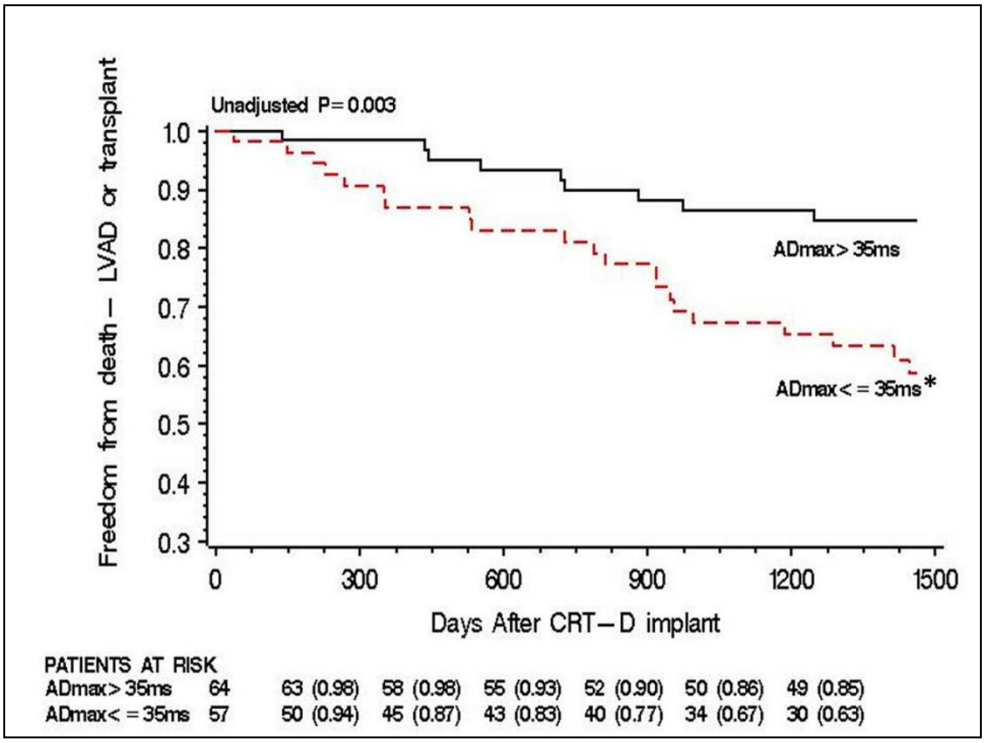


Figure 5. AD-max in relation to outcome

The Kaplan–Meier curves of freedom from death, left ventricular assist device or heart transplant after cardiac resynchronization therapy in relation to the AD-max. Patients with mechanical dyssynchrony had a more favorable outcome than those without.

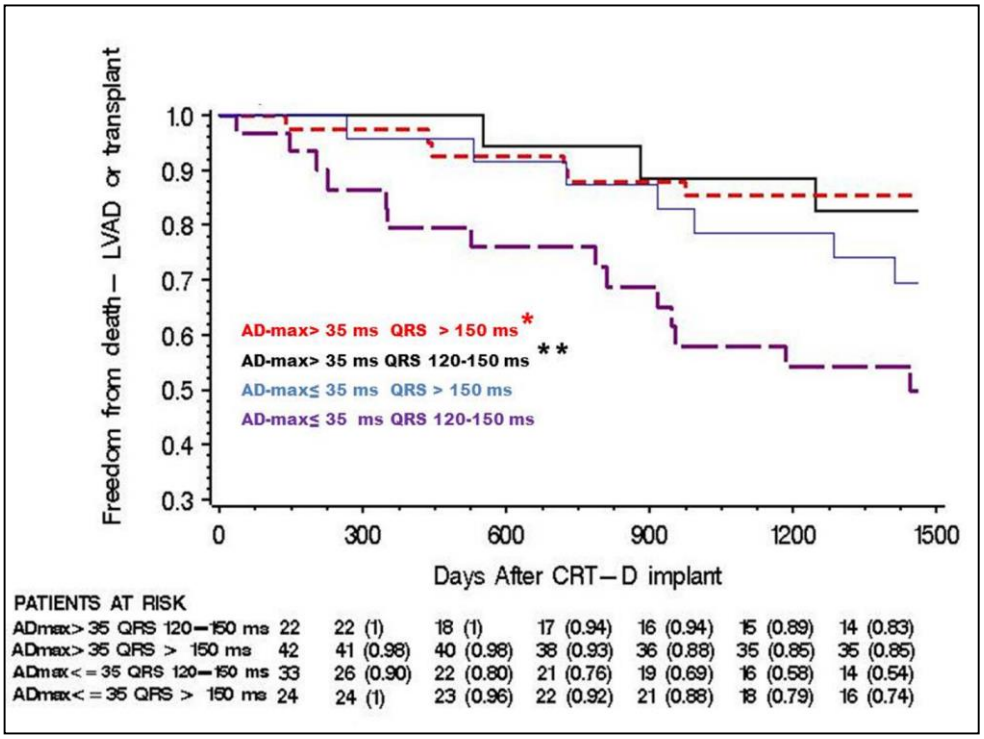


Figure 6. Mechanical dyssynchrony and QRS in relation to outcome

*Kaplan–Meier curves showing the probability of freedom from death, left ventricular assist device or heart transplant when patients were subdivided by baseline QRS duration and mechanical dyssynchrony evaluated by AD-max. Note the particularly poor prognosis of patients with QRS duration between 120 and 150 ms without dyssynchrony (*p < 0.01 when compared with AD-max >35 ms and QRS-duration between 120–150 ms).*

When differences between dyssynchrony methods were tested, AD-max > 35 ms had a superior association to outcome compared with time-to-peak methods (p = 0.01, both, for difference between indices).
C-statistics for the corresponding multivariable models were 0.77 (95% CI 0.67–0.86), 0.70 (95% CI 0.6–0.82), and 0.65 (95% CI 0.53–0.77). Statistically significant differences could not be demonstrated between AD-max and the other indices (p = 0.3 compared with Yu-index and p = 0.07 compared with OWD).
For multivariate analysis each dyssynchrony parameter was added individually to the model including QRS > 150 ms and etiology. AD-max was the only parameter of dyssynchrony independently associated with response. CI= Confidence interval.
Adding AD-max > 35 ms to a 4-year 10% risk model including QRS > 150 ms, ischemic heart disease, and either Yu index ≥ 32 ms or OWD ≥ 80 ms caused significant net reclassification improvements. (For Yu index NRI = 0.3, p < 0.001, for OWD NRI = 0.27, p < 0.001), respectively. Improvements were driven by significantly increased specificity for event-free survival when AD-max was added to the models (p < 0.02, for both models).

Dyssynchrony and QRS

In subgroup analysis patients without dyssynchrony in the narrower QRS group (120-150 ms) showed very poor outcome (Figure 6). Hazard Ratio was 4.29 (95% CI 1.46–12.59), p = 0.008, compared to patients with AD-max > 35 ms and QRS between 120 and 150 ms; and 4.03 (95% CI 1.91–8.51) compared to patients with AD-max > 35 ms and QRS > 150 ms, p < 0.001. There was a borderline significant interaction between QRS duration and AD-max (p = 0.07).
With regards to QRS-morphology, AD-max had a superior predictive ability compared to LBBB in the multivariable model (p = 0.04).

RESULTS - PAPER III

Analysis of 2DS-SD and TDI-SD was feasible in all 12 LV segments in 30/33 (90%) patients, and in 32/33 (97%) patients for AD-max. Reproducibility was best for AD-max (table 1 and 2).
Benefit from re-optimization by LVOT VTI at six months
The optimal setting determined by LVOT VTI at day one had changed after six months. Significant hemodynamic improvements were observed from VV-optimization compared to both this initial setting (LVOT VTI difference 15.2 (12.8-16.6) cm to 16.1(13.9-18.1) cm, p < 0.001) and compared to default simultaneous setting at six months, (15.6 (13.1-16-6) cm to 16.1(13.9-18.1) cm, p =0,001). Responders and nonresponders obtained similar benefit (p =0.52 for difference). 5/12 (42%) non-responders and 7/18 (39%) responders showed a relative increase in LVOT VTI > 10%. (p =0.87, for difference).

Mechanical dyssynchrony and VV-optimization

The best synchrony for the overall group of patients was found at LV pre-activation by 20 ms when assessed by AD-max and TDI-SD, but at simultaneous pacing when assessed by 2DS-SD (and by LVOT VTI) (Figure 7). VV-optimization by any of the indices most commonly resulted in LV pre-activation and rarely RV pre-activation. As expected, the larger the electrical delay was programmed from the optimal setting the more mechanical dyssynchrony was induced (Figure 8). Notably, the optimal setting was not the same when determined by different dyssynchrony methods and individual variations were large. The agreement between dyssynchrony indices in determining the optimal setting was moderate to good; κ = 0.62 for AD-max and TDI-SD, κ= 0.63 for AD-max and 2DS-SD and κ = 0.49 for 2DS-SD and TDI-SD.

Table 3. Univariate and multivariate risk analysis of mortality after CRT

Univariate analysis			
	HR	**95% CI**	**p-value**
Age > 65	1.4	0.68-2.80	0.35
Non-LBBB	2.34	1.17-4.68	0.02*
Female	0.79	0.33-1.93	0.61
Ischemic etiology	2.36	1.06-5.27	0.03*
QRS ≤ 150 ms	2.01	0.99-4.01	0.05
LVEF < 22 %	1.42	0.71-2.84	0.32
eGFR < 60	1.64	0.79-3.4	0.18
AD-max > 35 ms	0.26	0.11-0.58	0.001*
OWD ≥ 80 ms	0.49	0.23-1.04	0.06
Yu index ≥ 32 ms	0.46	0.19-1.13	0.09
Multivariate analysis each index added individually			
AD-max > 35 ms	0.35	0.16-0.77	0.01*
Yu index ≥ 32ms	0.49	020-1.20	0.12
OWD ≥ 80 ms	0.53	0.25-1.11	0.09

For multivariate analysis each dyssynchrony parameter was added individually to the model including QRS > 150 ms and etiology. AD-max was the only parameter of dyssynchrony independently associated with response. CI= Confidence interval.

Dyssynchrony was significantly reduced by VV-optimization when performed by any of the three indices compared to simultaneous pacing; 11.6 (8-24) ms vs. 7.5 (0-15) ms by AD-max, 41.1 (32.2-50.7) ms vs. 34.6 (24.3-46.1) ms by TDI-SD and 50.2.3 (43.3-57.3) ms vs. 45.3 (39.7-51.7) ms by 2DS-SD (p < 0.001, all). Better synchrony was obtainable in responders compared to non-responders when evaluated by AD-max (3.6 [0-7.6] ms vs. 15.4 [7-23.8] ms, p=0.01). Such differences were not present when evaluated by time-to-peak dyssynchrony measurements.

Relation between mechanical dyssynchrony and hemodynamic performance

Improved synchrony, by any index, translated into significantly improved hemodynamic performance (median of differences, 95 % CI): 1.35 (0.85-2.1) cm (p < 0.001) by AD-max, 1.2 (0.7-1.8) cm (p < 0.001) by 2DS-SD and 1.0 (0.4-1.7) cm, p=0.005) by TDI-SD as compared to simultaneous setting (Figure 9). Optimization using AD-max caused a higher LVOT VTI compared to TDI-SD 0.7(0.1-1.7) cm, (p= 0.02), and 2DS-SD, (0.7 (-2.75-1.1) cm, although the latter difference was not significant (p=0.23). Weighted kappa-statistics for the three dyssynchrony indices when compared to

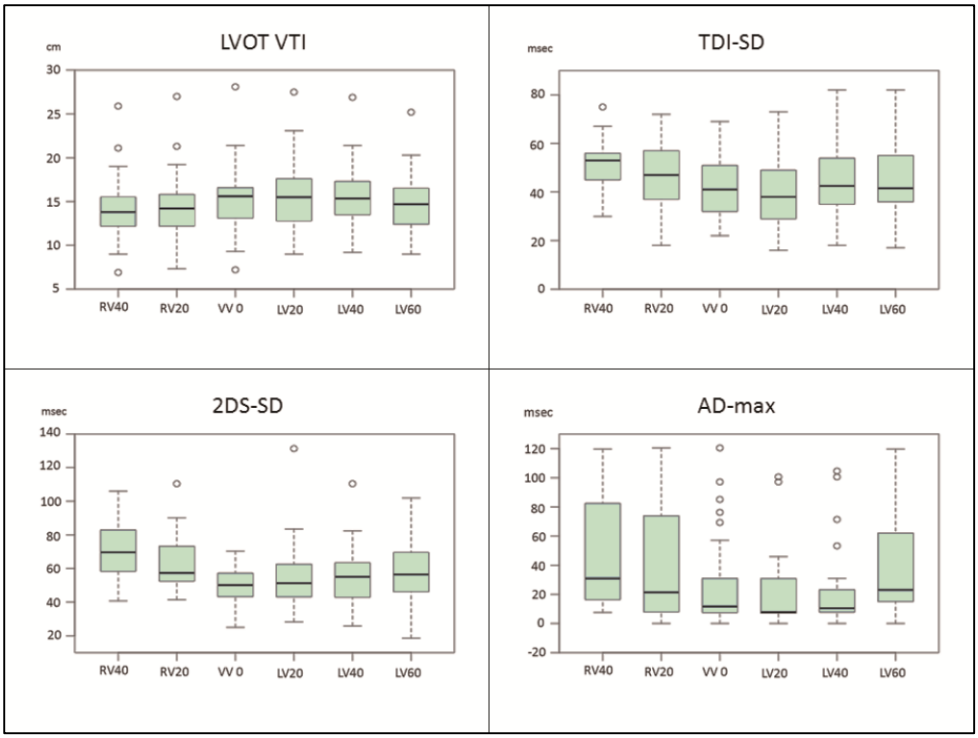


Figure 7. Variation in mechanical dyssynchrony and LVOT VTI at different interventricular delays.
The distribution of mechanical dyssynchrony and LVOT VTI measured by each method at different interventricular delays at six months. All variables are shown as median values with interquartile range and 95 % confidence intervals.

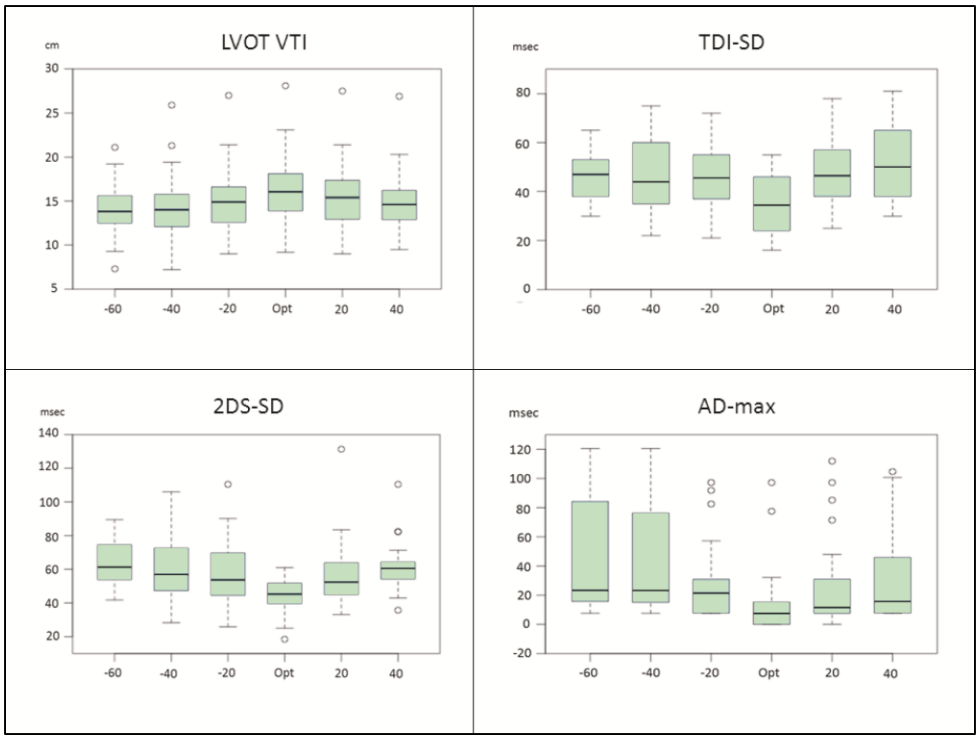


Figure 8. Mechanical dyssynchrony and LVOT VTI at the optimal setting and at steps of 20 ms above and below. Each variable shown at the optimal setting (Opt) and at steps of 20 ms above and below. The positive direction is defined as earlier LV activation. All variables are shown as median values with interquartile range and 95 % confidence intervals.

LVOT VTI were: 0.71, 0.62 and 0.55 for AD-max, 2D-SD and TDI-SD, respectively.

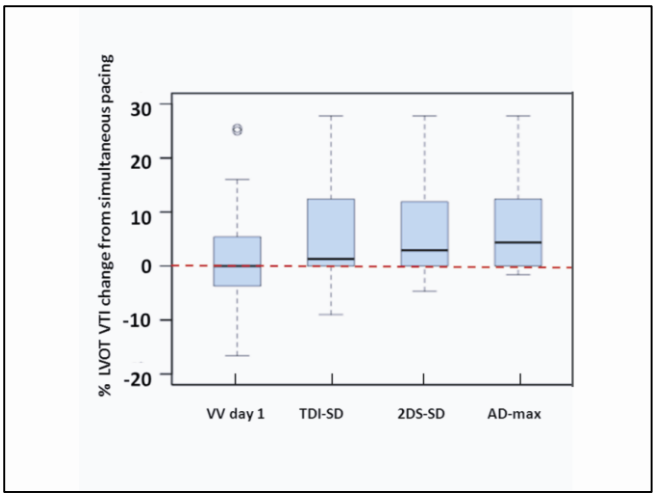


Figure 9. Increase in LVOT VTI by different optimization methods at six months. *Increase in LVOT VTI at six months when optimization was performed by different indices of mechanical dyssynchrony. VV day 1; optimal VV-setting as suggested day 1 by LVOT VTI, TDI-SD; optimal setting by TDI-SD, 2DS-SD; optimal setting by 2DS-SD, AD-max; optimal setting by AD-max. Red line corresponds to LVOT VTI at default simultaneous pacing. All variables are shown as median values with interquartile range and 95 % confidence intervals.*

DISCUSSION

Strain patterns and prediction of response: Paper I

Identification of activation delay by strain-patterns

Understanding the fundamental mechanisms of CRT is critical for improved evaluation of mechanical dyssynchrony. Mechanical dyssynchrony' may have various causes, but not all of these disturbances represent a substrate amenable to biventricular pacing. [9, 73] The target for CRT is likely an activation delay causing mechanical dyssynchrony. [9] Accordingly, the idea behind evaluation of contraction patterns in paper I was an attempt to specifically identify activation delay-induced mechanical dyssynchrony and relate such patterns to response.

Paper I showed i) that contraction patterns reflective of a significant LV activation delay are highly predictive of response, ii) LV remodeling is dependent on short-term redistribution of strain between early and late activated regions and iii) an approach based on pattern-analysis can improve current methods for dyssynchrony analysis.

Animal studies have demonstrated how activation delays, induced by RV or LV-only pacing cause a characteristic reciprocal opposing wall motion[37, 68] and that such wall motion leads to LV deterioration.[37, 40, 68, 74] In case of a "true" LBBB, or mimicked by RV-pacing, the contraction pattern is characterized by early contraction in early activated walls (septum) and pre-stretch followed by late contraction in late activated walls (lateral wall). Similar wall patterns, reversible to CRT, have been described in humans with LBBB.[67] However, the predictive ability of identifying such strain patterns, reflective of a LBBB-related activation delay, has never previously been tested.

The presence of a 'classic' (activation delay-induced) strain pattern was highly predictive of response to CRT, while other patients with wall patterns inconsistent with a LV activation delay were unlikely to benefit. In comparison, time-to-peak methods did not perform as well in this study, indicating a benefit of more specifically identifying the substrate for CRT. Importantly, the presence of a classical pattern significantly added to other predictors of response (etiology and QRS > 150 ms) further emphasizing a valuable role for pre-implantation assessment of mechanical dyssynchrony by this approach.

Mechanics of CRT response

Dyssynchronous activation of the LV creates an imbalance in regional loading conditions. The early activated region contracts first, against low chamber pressures and dissipates most of its energy into stretching the opposing, not yet activated walls. By the time the delayed walls are activated, the increased preload obtained in this region causes the walls to contract with increased force (the Frank Starling mechanism) and late peak contraction is observed. This again causes contraction in early activated regions to terminate prematurely.[67, 68] Accordingly, when assessed by In support, paper I demonstrated a significant increase in septal strain among responders at day one. In non-responders of whom the majority does not have a significant activation delay, such changes were not observed. Accordingly, the results propose an important role for immediate redistribution of regional strain in promotion of reverse remodeling.

In line with previous studies, both responders and non-responders showed significantly improved time-to-peak dyssynchrony to similar levels one day after CRT[77] and this effect was sustained during treatment.[78] These observations suggest that alignment of peak motion alone cannot explain all benefits from CRT. It is evident from this study why patients with similar time-to-peak differences at baseline may respond very differently to CRT. Thus, identifying contractile patterns reflective of an actual activation delay, rather than just measuring out the time-to-peak difference, holds additional prognostic information.

The idea of evaluating regional contraction patterns to predict response to CRT is not new and septal contraction has been the special center of attention. Patients with contraction during the pre-ejection phase (i.e. septal flash) generally have potential for large improvements,[79, 80] but this phenomenon does not identify all responders.[79] The current study supports the high predictive ability of a septal flash but more importantly, patients with early septal contraction outside the pre-ejection phase, in the presence of a classical pattern, may also respond.

Recent studies based on computer simulations suggest that the timing of septal contraction is mainly determined by the degree of activation delay and regional contractility in opposing walls. [81] Identifying a classical contraction pattern as an indicator of a true activation delay likely requires some degree of preserved contractility in late activated walls in order for early termination of septal contraction to be present. Consequently, a classical pattern appears to hold inherent information with regards to regional viability which may add to the predictive value of this approach.

Other groups have proposed evaluation of contraction patterns in prediction of response to CRT. Indices reflective of opposing wall motion such as discoordination, (i.e. opposing wall stretch and contraction) [82] and indices based on identifying early septal contraction such as septal flash[79, 80] and TDI-derived transverse apical motion[83] have shown promise in prediction of response to CRT. Among these, cross-correlation analysis (XCA)

represents a more mathematical approach[51, 84] which was further studied in Papers II and III.

Mechanical dyssynchrony by cross-correlation analysis and association with long-term outcome: Paper II

XCA is a more quantitative method for dyssynchrony analysis particularly sensitive to opposing wall motion, [51] which as demonstrated in paper I is a key-element in understanding and identifying activation delay-induced heart failure amenable to CRT. In addition, XCA shows potential for reducing the subjectivity of wave form analysis by including more data-points in the analysis. [51, 84] This may offer an additional level of precision as compared to relying on single time-point measurement of the complex waveforms of mechanical cardiac movement. Thus, potentially this method may overcome limitations raised by PROSPECT and others.[55-57]

Paper II showed i) that baseline mechanical dyssynchrony assessed by XCA is strongly associated with favorable outcome after CRT, ii) assessment of mechanical dyssynchrony may be of particular value for patients with intermediate QRS-duration and iii) XCA of myocardial acceleration has a significantly stronger association with outcome than other tissue Doppler-based methods. Complex waveform comparisons by mathematical modeling for similarities or differences due to time offsets may be difficult to understand and apply. The purpose of XCA in evaluation of mechanical dyssynchrony is to answer a simple question: How similar are two waveforms?

XCA for assessment of mechanical dyssynchrony was recently validated and its ability to better discriminate wall motion abnormalities caused by other diseases from those caused by dyssynchrony as well as the ability to predict LV remodeling has been established.[51] The association of mechanical dyssynchrony with long-term outcome using XCA was tested based on a pre-defined cut-off for AD-max > 35 ms. The presence of mechanical dyssynchrony by AD-max before CRT-implantation was highly associated with survival free from death, LVAD and heart transplantation. In addition, this dyssynchrony parameter was found to be superior to other established TDI-derived parameters of longitudinal dyssynchrony. Net reclassification improvement analysis suggested that adding AD-max> 35 ms to a predictive model including QRS ≥ 150 ms, ischemic heart disease, and either of the two time-to-peak dyssynchrony indices tested in this study caused significant improvements in risk classification. In particular, the ability to identify patients with low risk of death, HTX or LVAD was improved. Although this finding must be cautiously interpreted as the risk categories are based on a somewhat arbitrary choice of categories, it supports the assumption that XCA may provide a more specific analysis for identification of activation delay-induced heart failure.

Few studies to date have investigated the association between baseline mechanical dyssynchrony and long-term outcome,[23, 24, 49, 54, 85] and few have followed patients for a period of 4 years. [23, 49] In support of our findings, studies have shown that baseline mechanical dyssynchrony is a marker of more favorable outcome after CRT. One study clearly showed the importance of mechanical dyssynchrony for long-term outcome by testing four different indices of mechanical dyssynchrony which were all significantly associated with event-free survival.[23] Among these, the commonly used Yu-index > 32 ms and OWD ≥ 80 ms, although only Yu index was found to be independently associated with outcome after adjustment for co-variates QRS > 150 ms and ischemic heart failure. In this study, borderline significant associations were demonstrated for Yu-index and OWD. While lack of a significant association for these indices may partly be ascribed to the relatively small sample size, more importantly, applying XCA to the same velocity data significantly improved the association between mechanical dyssynchrony and outcome. These results suggest that XCA can provide improved dyssynchrony analysis of TDI-derived velocity data.

Mechanical dyssynchrony and QRS

It may be that assessment of mechanical dyssynchrony will only have a limited role in patients with QRS-duration > 150 ms, as these patients have a large a priori likelihood of response.[86] A recent meta-analysis including the five largest CRT-trials showed that patients with QRS-duration greater than 150 ms had a reduction in heart failure events from CRT, whereas those with a QRS less than 150 ms did not.[87] Although this analysis had some limitations, [88] it supports additional refinement of current criteria in patients with intermediate QRS between 120-150 ms. The importance of mechanical dyssynchrony by AD-max in relation to QRS-duration was demonstrated in subgroup analysis. A particular poor prognosis was observed among patients who lacked mechanical dyssynchrony and had a QRS-duration between 120-150 ms suggesting a role for dyssynchrony evaluation in these patients. These findings are in line with those of Gorcsan et al. who demonstrated similar poor outcomes for patients with absence of mechanical dyssynchrony whether evaluated by radial speckle tracking or TDI-velocity measurements, respectively.[23] Studies are currently being conducted which will explore the value of mechanical dyssynchrony for patients with even narrower QRS-duration.[89]

QRS morphology may be equally important as QRS duration,[90] and this is now reflected in CRT- guidelines.[20, 21] The MADIT-CRT trial recently showed that non-LBBB patients do not have the same clinical benefit from CRT as patients with LBBB.[19] As proposed by the authors, this may be explained by a lesser degree of dyssynchrony among non-LBBB patients compared to patients with LBBB.[91] In support, a very low percentage of patients with dyssynchrony in the non-LBBB group compared to patients with LBBB were found in this study when evaluated by AD-max and other have reported similar findings.[91] These observations make 'physiologic sense' as patients with other conduction abnormalities than LBBB presumably have normal activation of the left ventricular Purkinje system.[36] This has been recognized by the FDA and for patients in NYHA I and II device labeling is now restricted to those with LBBB. Interestingly, evidence has recently been presented suggesting that not all patients with LBBB by ECG have a complete LBBB.[36] Endocardial mapping studies[92, 93 and observational ECG series[94] suggest that around 1/3 of patients have a normal LV activation time. This is supported in Paper I, in which almost 1/3 of patients did not have mechanical evidence of a complete LBBB, despite evidence of LBBB by conventional ECG criteria. In this study (Paper II) a superior association for AD-max with favorable outcome compared to LBBB was found. Thus, it may be that evaluation of mechanical dyssynchrony has a role even in patients with LBBB at this point. However, new ECG-criteria have been proposed and the potential value in selection of CRT-candidates and the role for assessment of mechanical dyssynchrony remain to be established in future studies.

Optimization of mechanical synchrony: Paper III

Optimization of the interventricular programming delay

Patients receiving a CRT-device, may not obtain optimal resynchronization from default simultaneous pacing. This may be due to individual differences in the extent of fibrosis or scar,[95] lead placement[96] or variations in activation pathways of the LV.[92] These factors can to some degree be compensated for by tailoring the interventricular programming delays (VV-optimization). However, the use of this procedure is controversial and a role for evaluation of mechanical dyssynchrony is not well established.

Paper III showed that i) VV-optimization at six month can benefit both responders and non-responders to CRT, ii) improvements in mechanical synchrony by any index translated into improved hemodynamics and iii) XCA showed the best feasibility, reproducibility and correlation to hemodynamic performance.

The majority of patients in Paper III had a different optimal setting after six months compared to day one. Around 40 % obtained more than 10 % increase in LVOT VTI from sequential pacing compared to default simultaneous pacing and improvements were observed among both responders and non-responders. In line with reports from a number of single-center studies[97-104] these findings indicate that VV-optimization may benefit some patients. Multicenter studies, however, have not been able to establish a role for VV-optimization and the procedure remains controversial. [105, 106] It may be that the relatively small changes observed do not translate into changes in LV remodeling response or functional parameters (which have been the primary endpoints tested) and the effect on long-term outcome has never been investigated. Another reason could be the choice of method for VV-optimization in previous studies which may not have been optimal.

VV-optimization and mechanical dyssynchrony

It is unclear whether VV-optimization should be guided by LV function parameters or dyssynchrony assessment.[99] A number of methods have been proposed for this purpose, among these, device based algorithms,[107] ECG based optimization[101] and echocardiography with assessment of hemodynamic parameters[102, 108] or mechanical dyssynchrony.[100] Assessment of mechanical dyssynchrony is appealing as mechanical resynchronization is considered to be the primary mechanism behind response to CRT.[23] Tissue Doppler time-to-peak indices have been the most frequently used for VV-optimization,[98, 100-102, 104, 109] while data regarding other methods for dyssynchrony assessment are sparse. In line with the considerations in Papers I and II, the use of XCA in VV-optimization was tested and compared to time-to-peak indices based on TDI-derived velocities and 2D-strain analysis, respectively.

The findings revealed several relationships that were independent of the method chosen for dyssynchrony analysis.

First, a close relationship between activation delay and mechanical contraction was demonstrated by use of all three methods. The larger the delay was from the optimal setting the more mechanical dyssynchrony was induced.

Second, Improvements in mechanical dyssynchrony by any dyssynchrony method translated into improved hemodynamic performance as measured by LVOT VTI. These observations confirm the current understanding that activation delays induce mechanical dyssynchrony and that resynchronization of such mechanical dyssynchrony leads to improved LV function.[19] Although proposed in other studies,[98, 102, 110] this has not previously been demonstrated using several different methods for dyssynchrony analysis.

Third, in line with previous studies LV pre-activation was most frequently the suggested optimal programming delay when assessed by any of the three indices.[98, 99, 103, 109]

Despite these similarities, the methods were not interchangeable for the purpose of VV-optimization. Responders obtained significantly less dyssynchrony compared to nonresponders when assessed by AD-max, while no differences were observed when measured by time-to-peak methods. Moreover, AD-max showed higher feasibility, reproducibility and a higher agreement with LVOT VTI compared to the other indices. Thus, some hierarchy seems to exist amongst different indices for VV-optimization.

In accordance with study II and III, the findings indicate that XCA provides improved assessment of dyssynchrony and for the purpose of VV-optimization represents a more robust quantitative index.

Dyssynchrony assessment can be improved: Extending time-to-peak

The conventional time-to-peak indices investigated in this thesis did not fare as well in prediction of response to CRT or for the purpose of VV-optimization as methods more closely related a significant LV activation delay (i.e. pattern-based analysis and XCA). This observation does not refute previous studies reporting the value of mechanical dyssynchrony by time-to-peak indices. It does, however, show that echocardiographic assessment of dyssynchrony can be further developed and improved.

Although seemingly easy and simple to perform time-to-peak indices have certain inherent limitations. First, the indices are highly user-dependent both regarding image acquisition and analysis. The indices are highly susceptible to small changes in region of interest location and it may not always be straightforward to assess which peak reflects which motion and some degree of subjectivity is inevitable.[9, 57] The inclusion of more data-points rather than relying on single time-points reduces variability and improves accuracy.[59] XCA represents such a method by using data-points from the entire systole and the calculations are automated.[51] The reproducibility of time-to-peak indices reported in the current thesis was found to be reasonable overall and in line with reports from other groups.[23, 49, 102] However, a higher reproducibility was obtained with XCA compared to TDI-derived time-to-peak indices in both Paper II and III despite being based on the same velocity traces.

Second, a time-to-peak approach does not include any information on the nature of the wall deformation. Significant time-to-peak differences can be caused by activation delays between walls, but similar time-to-peak differences may also be due to regional differences in contractile force and duration.[9] The latter, as demonstrated in Paper I is unlikely to benefit from CRT, thus this distinction is important. Relatively large time-to-peak differences can be observed in the absence of a true activation delay, in particular among patients with ischemic heart failure due to areas of scar tissue[61] and patients with exacerbation in heart failure or other conditions causing changes in loading conditions. [60, 111] Specifically addressing the contraction patterns improves the ability to identify a substrate amenable to CRT as proposed in Paper I. Other methods like XCA which are sensitive to this opposing wall motion may also provide a more specific assessment in this regard.

LIMITATIONS

Specific limitations exist for each manuscript but general limitations should be mentioned. First, the designs of the three studies

are limited. None of the studies were randomized, and the study populations were relatively small. Paper II was a retrospective study, and there was no comparison to patients who did not undergo CRT. Consequently the direct benefit from CRT cannot be precisely determined. The findings of the current thesis should not yet be used to supplant established clinical guidelines or criteria for CRT therapy as prospective and randomized studies are warranted.

Second, no data concerning radial strains were included in these investigations. Studies have demonstrated the use of time-to-peak radial strain by speckle tracking for dyssynchrony analysis and this method may have a better correlation with different outcomes than descriptors of longitudinal function.[23, 49] Images for radial strains analysis were not consistently acquired, thus comparisons were not possible. However, the inherent limitations discussed for the-time-to-peak approach likely apply to any modality including speckle tracking in the radial direction. Of note, assessment of radial function has not clearly been demonstrated to be superior to the assessment of longitudinal function, [46] and radial speckle tracking has yet to be compared to new indices of longitudinal function.

Third, other important determinants of CRT response such as the scar burden[112, 113] and lead placement[96, 114] were not assessed in detail in this thesis. Assessment of mechanical dyssynchrony in patients with scar areas can be particularly challenging, and should be subject to future studies.

Regarding the individual manuscripts:

Paper I: The evaluation of strain patterns is only semi-quantitative at the moment. No simple number can classify patients along what is a continuum of disease, and although time-to-peak indices have the advantage of a single number they did not perform as well in predicting outcome in comparison to pattern analysis. By definition, a heterogeneous pattern now loosely incorporates all patterns that are nonclassic. There may be unrecognized hybrid patterns within this group not yet identified. In addition, suggestions are that subgroups of classical patterns may hold additional prognostic information although this is still largely unexplored.

While a ´pattern-approach´ to evaluate mechanical dyssynchrony may seem complex, practical experiences indicate there is little difficulty in teaching this method to fellow physicians and sonographers. Implementation of this method appears less troublesome than proper analysis of time-to-peak TDI waveform determination.

At the very least, Paper I offers a logical explanation why some patients respond to CRT and others do not and provides a rationale for a more physiologic approach to dyssynchrony assessment.

Papers II and III: Cross-correlation analysis may not reflect all physiologic subtleties inherent in mechanical dyssynchrony. Finding a single index that can be used in the quantification of the complex mechanical impairments encountered in activation induced heart failure patients is difficult. XCA has a unique appeal in that it integrates multiple points along any complex waveform line and is not dependent on single point-point measurements as found in time-to-peak analysis. In addition, it is sensitive to opposing wall motion. However, generation of velocity tracings takes as much skill and experience as other TDI analyses. The calculation spreadsheet is now available for XCA[115] but the method is still not an integrated part of commercially available software packages.

Paper III: The exact role for XCA is not known and it should now be tested in a larger, prospective study. Measurements were compared to LVOT VTI which is currently the standard for echocardiographic evaluation of hemodynamic performance. However this method has its own limitations including the criticism that it cannot be performed reproducibly. It was not possible to investigate whether VV-optimization by mechanical dyssynchrony was superior to the use of LVOT VTI, because VTI was used as a reference. Although the data suggests that benefit can be derived through responders and non-responders alike, it remains to be determined whether this benefit will translate into long-term outcome benefit

CONCLUSIONS

In this thesis the performance of new echocardiographic methods for evaluation of mechanical dyssynchrony was investigated in three different studies. The aim was to apply methods, which better reflect significant activation delays, thought to be the substrate for CRT.

The main findings can be summarized as follows:

Echocardiographic LV dyssynchrony assessment by identification of distinct strain patterns, which better reflect a true activation delay, is highly predictive of response to CRT. Response to CRT is characterized by acute reversal in strain between early and late-activated regions. (Paper I)

Mechanical dyssynchrony by XCA is closely associated with favorable long-term outcome to CRT. Assessment of mechanical dyssynchrony may be particular important in patients with intermediate QRS-duration. (Paper II)

Repeating VV-optimization after six months of CRT is beneficial in both responders and non-responders. Improvements in mechanical synchrony by any index translated into improved hemodynamics. Of the tested methods for echocardiographic dyssynchrony evaluation, XCA showed the best feasibility, reproducibility and correlation to hemodynamic performance. (Paper III)

All three studies concurrently showed that evaluation of strain-patterns and XCA provides improved dyssynchrony analysis compared to conventional time-to-peak indices. (Paper I, II and III)

In conclusion, this thesis demonstrates and confirms the importance of mechanical dyssynchrony for treatment with CRT. New methods for assessment of mechanical dyssynchrony, from semi-quantitative (pattern analysis) to more thorough quantitative comparison of waveforms (cross-correlation), which better reflect significant LV activation delay, can provide improved tools for dyssynchrony analysis. Consideration of strain or TDI detected contraction by waveform analysis offer opportunities to extend the use of ultrasound methods in understanding and determining mechanical dyssynchrony beyond time-to-peak methods.

CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES

More than 100 studies have now been published supporting the idea that correction of the delayed electrical activation that results in mechanical dyssynchrony is the primary mechanism behind short or long term favorable response to CRT. Since a third of CRT patients fail to benefit from such therapy, current indications for CRT need to be improved. In addition, other patients groups beyond current guidelines may also benefit from this treatment. To date, however, the value of patient selection based on current methods for detecting the presence of mechanical dyssynchrony has had limited success and has not been demonstrated in large clinical trials.

Reasons for the limited success are manifold. First, technology and diagnostic methods are rapidly changing. When landmark clinical trials were planned and initiated, methods for dyssynchrony assessment were early in their technologic development. Second, it takes training and experience to implement or evaluate the results of these new types of diagnostic testing. Every diagnostic method requires suitable training, experience and understanding of the method before consistent implementation can be achieved. Third, we may not be adequately measuring the actual altered physiology present in patients with activation delay-induced heart failure. At present, there is broad acceptance of the concept that electrical activation delays cause disordered mechanical contraction. However, we have yet to unravel the complexities of electrical-mechanical coupling and the dynamic relationships between different wall segments during the entirety of the cardiac cycle. There may be different kinds of mechanical dyssynchrony that require other yet unrealized therapeutic interventions given variations in segmental contraction/stretch,

The studies presented in this thesis represent some limited steps to extend the boundaries of time-to-peak methods to broaden our understanding of mechanical dyssynchrony. While these methods require further refinement and validation and are not yet ready for clinical implementation, the improved performance by a more complete assessment of entire waveforms is intriguing and highly encouraging.

The value of strain-pattern assessment described in this thesis have stimulated investigations in other patients with heart failure specifically those with dual-chamber pacemakers and patients with congenital heart disease who have systemic right ventricles as a result of birth defect or surgical correction. Initial results in both patient groups are promising.

XCA has now been tested in different set-ups and should be tested in larger prospective studies with regard to long-term outcome. We have already initiated such studies.

Parameters of dyssynchrony assessment will likely continue to develop over time. The work in this thesis is extending into applications for new ultrasound technology such as the high speed, fifth generation scanner being developed at Duke University. This system overcomes the relatively slow frame rates of conventional ultrasound machines that limit the detection of rapidly moving cardiac events. At frame rates between 500-1000 fps new phenomena can be observed directly related to electrical events. If true, such methods may dramatically increase understanding of altered physiology of disorders of activation-contraction coupling and be of value for future evaluation of mechanical dyssynchrony. Interesting are also comparisons of the patterns of strain in the original subjects included in Paper I to their 12-lead ECGs. As discussed, not all LBBB's are the same and it has recently been suggested that LBBB by ECG should be redefined to separate out those with potentially correctable conduction delays. Initial comparisons have indicated, for the first time, that there is an association between the proposed new ECG criteria and the classic strain pattern.

What started as a limited research proposal involving detailed and restrictive measurements resulted in a broad and new found personal exploration into activation delay-induced heart failure and its altered physiology. However limited the findings, a certain logic ties the various projects together and presents new opportunities for continued study.

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SUMMARY

Background

Cardiac Resynchronization Therapy (CRT) significantly reduces morbidity and mortality in patients with symptomatic severe heart failure and evidence of interventricular conduction delay by ECG. Unfortunately, one third of patients do not respond to CRT and selection criteria may need to be improved. Assessment of mechanical dyssynchrony by echocardiography has been suggested to add value in selection of CRT candidates. However, current methods for dyssynchrony analysis may not accurately reflect an activation delay amenable to CRT and controversy remains for the role of mechanical dyssynchrony.

Hypothesis

This thesis was based on the assumption that benefit from treatment with CRT requires a significant activation delay of the left ventricle (LV). It was hypothesized that echocardiographic methods for evaluation of mechanical dyssynchrony, reflecting this fundamental pathophysiologic change, could predict response to CRT. In addition, it was hypothesized that this approach would provide improved diagnostic value with regards to dyssynchrony analysis compared to conventional time-to-peak measurements.

Methods

Three studies were performed and consisted of:

1) A prospective study in 67 consecutive patients who fulfilled standard criteria for CRT and had left bundle branch block (LBBB) by ECG. Patients underwent 2D-strain echocardiography (speckle tracking analysis) one day prior to CRT, at day one and six months after implantation and the mechanics behind CRT-response was studied. Strain patterns thought to reflect a complete LBBB was characterized and the predictive ability of this approach was tested with regards to echocardiographic response at six months (> 15 % reduction in LVESV) and compared to current time-to-peak indices.

2) A retrospective study in 131 consecutive patients from two centers. Patients all had a Tissue Doppler Imaging (TDI)-dyssynchrony study prior to implantation. Baseline mechanical dyssynchrony was determined by cross-correlation analysis (XCA), a more quantitative method for comparison of contraction patterns, and the association with long-term outcome (survival free from LVAD or heart transplantation after four years) was determined and compared to current time-to-peak indices. In addition, subgroup analysis of the relation to QRS-duration was performed.

3) A prospective study of 33 consecutive CRT-recipients. Patients were VV-optimized at day one after implantation. At six months,

TDI and 2D-strain analysis were performed at 6 different interventricular pacing intervals in steps of 20 ms to investigate the performance of different indices of mechanical dyssynchrony (time-to-peak indices and XCA, respectively) and the relation between mechanical dyssynchrony and hemodynamic performance by LVOT VTI.

Results

1) A LBBB-related strain pattern was highly predictive of LV remodeling response to CRT at six months and significantly added to other known predictors of outcome (etiology and QRS> 150 ms). A reversal in strain-ratio between the early and late-activated myocardial regions was observed at day 1 only among responders suggestive of an important role in promotion of remodeling.
2) Mechanical dyssynchrony at baseline measured by XCA was independently associated with improved long-term outcome in CRT-recipients. Patients with lack of mechanical dyssynchrony and QRS between 120-150 ms showed particularly poor outcome.
3) VV-optimization after six months of CRT was beneficial in both responders and non-responders. Improvements in mechanical synchrony by any method translated into improved hemodynamics. XCA showed the best feasibility, reproducibility and correlation to hemodynamic performance.
In all three studies, new methods for dyssynchrony assessment performed better compared to conventional indices.

Conclusions

This thesis confirms the importance of mechanical dyssynchrony for outcome to CRT and demonstrates the value of dyssynchrony assessment for prediction of response to CRT as well as in optimization of device programming. New methods, which better reflect a significant LV activation delay, provides an improved tool for dyssynchrony analysis compared to conventional techniques.

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