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Full Title:

Coupling of ventricular action potential duration and local strain patterns during reverse remodeling in responders and non-responders to cardiac resynchronization therapy

Short title: Coupling of APD and regional strain during CRT

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Abstract

Background: The high risk of ventricular arrhythmias in heart failure patients remains despite the benefit of cardiac resynchronization therapy (CRT). An electromechanical interaction between regional myocardial strain patterns and the electrophysiological substrate is thought to be important. **Objective:** We investigated the in-vivo relation between left ventricular (LV) activation recovery interval (ARI), as a surrogate measure of activation potential duration (APD), and local myocardial strain patterns in responders and non-responders to CRT. **Methods:** ARI were recorded from the left ventricular epicardium in 20 CRT patients 6 weeks and 6 months post implant. Two-dimensional speckle tracking echocardiography was performed at the same time to assess myocardial strains. Patients with ≥15% reduction in end-systolic volume at 6-months were classified as responders. **Results:** ARI reduced in responders, 263±46ms vs. 246±47ms, p<0.01; and increased in non-responders, 235±23ms vs. 261±20ms, p<0.01. Time-to-peak (TPS) radial, circumferential and longitudinal strains increased in responders (+41±27ms, +35±25ms, +56±37ms; p<0.01); and reduced in non-responders (-58±26ms, -47±26ms, -64±27ms; p<0.01). There was a non-linear correlation between changes in TPS and ARI (r≥0.70; p<0.01). Baseline QRS >145ms and QRS shortening with biventricular pacing was associated with ARI shortening during CRT. **Conclusions:** Changes in ventricular wall mechanics predict local APD lengthening or shortening during CRT. Non-responders have a worsening of myocardial strain and local APD. Baseline QRS >145ms and QRS shortening on biventricular pacing identified patients who exhibited improvement in APD.

Key Words: Cardiac remodeling, cardiac resynchronization therapy, activation recovery interval, action potential duration, myocardial strain

Introduction

Cardiac resynchronization therapy (CRT) has been demonstrated to provide symptomatic improvement, induce structural reverse remodeling and improve survival in heart failure patients with prolonged QRS durations.[1-3] However, approximately one third of patients do not derive benefit and the incidence of arrhythmias remains substantial.[4,5] The further understanding of the electromechanical changes during CRT therefore remains an important challenge.

The response to CRT in patients with broad QRS complex is generally considered to be multifactorial.[6] Several studies demonstrating the beneficial effects of CRT on LV remodeling have suggested that improvement of LV mechanical synchrony was the predominant mechanism,[7] while others have in addition focused on the molecular and cellular effects that it chronically induces.[8-10]

Information in humans is limited. We have recently reported activation recovery interval (ARI), as a surrogate measure of APD, changes in heart failure patients during CRT.[11] The clinical response to CRT is known to be closely linked to reversal of dyssynchrony.[12] Improved LV function by CRT has been shown to be associated with a reduced arrhythmia burden,[13] whereas persistent or new radial dyssynchrony or abnormal longitudinal strain is associated with an increased rate of ventricular arrhythmias or death.[14,15] The effect of LV resynchronization on the electrophysiologic substrate is a suggested mechanism. However, at present it has not been determined whether changes in APD during CRT relate to changes in regional mechanical function in humans.

We aimed to explore the relationship between LV APD and strain following LV reverse remodeling in response to CRT. To assess this we recorded ARI from the

epicardial CRT LV lead as a conventional measure of local APD together with speckle tracking analysis of regional ventricular strain at 6 weeks and 6 months following the initiation of CRT.

Methods

Study population and protocol

We prospectively studied 20 consecutive patients receiving CRT in our institution. All patients were invited to participate in the study in the pre-CRT assessment clinic, following local research ethics committee approval. The selection criteria included drug refractory symptomatic heart failure with New York Heart Association (NYHA) class II-IV, impaired left ventricular ejection fraction (LVEF) ≤ 35% with a QRS duration ≥ 120ms. Clinical status according to NYHA class and Minnesota heart failure questionnaires (MLHFQ) and echocardiographic measures of LV function were assessed pre and 6 months post CRT implant. Simultaneous echocardiography and LV unipolar electrogram (UEG) recordings were performed 6 weeks and 6 months post CRT implant to assess LV functional and electrical remodeling in response to CRT.

A positive LV functional response was defined as ≥ 15% reduction in LV ESV on TTE assessment coupled with improvement in clinical heart failure symptoms at 6 months post implant.

Functional remodeling assessed by transthoracic echocardiography

Transthoracic echocardiography was performed by independent operators who were blinded to the outcome of the electrical remodeling data using a GE Vivid 7 scanner

(General Electric-Vingmed, Milwaukee, WI, USA) at baseline, 6 weeks and 6 months post implant. Standard 2D images of LV dimensions in standard short axis and long axis views were acquired during breath-holds. LV volumes in end-systole (ESV) and end-diastole (EDV) were measured to estimate EF using the 2-dimentional modified biplane Simpson's method. Analysis was done on EchoPac 6.0.1 (General Electric-Vingmed, Milwaukee, USA). CRT device optimization was performed at 6 weeks post-implant as per our standard clinical protocol. At this time the AV and VV delays were adjusted under echocardiographic guidance using mitral valve inflow Doppler signals and aortic valve outflow velocity-time-intervals to achieve the best hemodynamic benefit. Fluoroscopic image acquisitions in right and left anterior oblique views during CRT implant were used to estimate the LV segment where the LV lead was positioned for each individual. Each segment was classified according to the American Heart Association 16 segment classification. Short axis and longitudinal images focusing on the AHA segment of LV lead position were acquired at 6 weeks and 6 months post CRT implant in preparation for off-line speckle tracking analysis in order to calculate the time (gated from the onset of QRS body surface electrocardiography complex) to peak radial, circumferential and longitudinal strain of the respective myocardial segment (see Figure 1A-C). Speckle-tracking analysis was performed using independent 2D Cardiac Performance Analysis software (TomTec, Unterschleissheim, Germany).

Figure 1

Electrical remodeling assessed by activation recovery interval, ARI, measurement

At 6 weeks and 6 months post CRT implant, a 30 second recording of the LV UEG signal was made via the device programmer (Merlin, St Jude Medical) during DDD-

RV or VVI-RV pacing, depending on whether the patient was in sinus rhythm or in atrial fibrillation. The data from our previous study implied that electrical remodeling may take place before 6 weeks, however, differences observed at 6 weeks were not statistically significant.[11] Others have observed these changes to be short term following initial CRT.[16] The adoption of measuring the interval between 6 weeks and 6 months allowed both electrical and anatomical modelling to establish before our measurements were taken. UEG recordings were made after at least 2 minutes of pacing at a constant rate of 10 beats above the patient's intrinsic heart rate. This enabled comparisons between patients with sinus rhythm and those with atrial fibrillation and eliminated the influence of heart rate on ARI. This is based on original work by Franz et al showing that adaptation to rate change approximates an asymptote by 2 minutes for a wide range of cycle length perturbations.[17] This is also the case for patients with atrial fibrillation as we ourselves confirmed in a more recent study.[18] The 30-second LV UEG recordings were analyzed off-line using a custom software script within MATLAB (MathWorks, Massachusetts, USA) to derive the ARI. ARIs were measured using conventional validated criteria from minimum dv/dt of the QRS of the UEG to maximum dv/dt of the local T wave as previously described,[11] see Figure 1D. As a local measurement of repolarization, ARI gave us a unique opportunity to study the regional changes in APD and strain

Statistical analysis

Continuous variables for the baseline characteristics were reported as mean ± SD and categorical variables as number (and percentage) of participants. Continuous variables were compared using the Wilcoxon rank test or Mann-Whitney U test for dependent or independent observations respectively. Categorical variables were compared using the Chi-squared test. Correlation between time to peak strain (TPS) and ARI were

expressed using Spearman's correlation coefficient. A p value < 0.05 was considered to be statistically significant. All statistics were performed using Prism version 6, (GraphPad software, California, USA)

Results

Study population

Twenty patients fulfilling standard indications for CRT participated and completed the study. In this cohort, 25% were female and the overall mean age was 61±12yrs. All of the patients were in NYHA class III or IV. The mean QRS duration was 143±21ms, 45% of the patients had an ischemic etiology and 55% dilated cardiomyopathy on the basis of World Health Organization criteria. The baseline characteristics of the patients including the positions of the LV leads are shown in Supplemental Table1 (Online supplementary data).

Left ventricular functional remodeling

At 6 months post CRT, LVESV reduction ≥15% occurred in 11 patients (55%), all of whom reported an improvement in heart failure symptoms (NHYA class reduction ≥ 1 class and quality of life questionnaires reduction of ≥20% in MLHFQ scores). These patients were considered to be positive responders with functional reverse remodeling. The mean LV ESV in the responders group improved from 177±87ml at baseline pre CRT implant to 107±51ml ($p<0.01$) at 6 months post CRT. The mean LV EF improved from 23±9% to 36±11%. In contrast, the mean LV EF in the non-responders group was 22±4% at baseline and 23±4% at 6 months post CRT. The

changes in clinical LV functional status between responders and non-responders at 6 months are shown in Table 1.

Table 1

Changes in LV electrical remodeling and time to peak strain

During the 6 months receiving CRT, all the patients (responders and non-responders) were paced via bipolar vectors (LV and RV). The pacing vectors and pacing outputs were not changed during the 6 weeks to 6 months post CRT implant study period. The percentages of the bi-ventricular pacing were the same between the two groups. There were no major differences between the optimized AV delays and VV delays between the responder and non-responders in the study cohort. Median AV delays were 130ms±10ms and 130±10ms in the patients with sinus rhythm in the responders and non-responder groups. Variations in VV delays between responders and non-responders group were not significantly different.

LV UEGs were recorded during DDD-RV or VVI-RV pacing at a fixed heart rate ranged from 70bpm to 100 bpm within the cohort (the same heart rates were maintained during recordings at 6 weeks and 6 months for individual patients; paced heart rate of the two patients with atrial fibrillation were 75bpm and 80bpm, which were similar to the other patients in sinus rhythm, mean 80bpm). There was a clear divergent change in ARI seen between CRT responders and non-responders from 6 weeks to 6 months post CRT implant. In the responders ARI decreased from 263 +/- 46 to 246 +/-47 ($p<0.01$) whereas in the non-responders ARI increased from 235+/-23 to 261+/-20 ($p<0.01$). (See Figure 2 and Table 2).

Figure 2

The corrected QT (QTc, Bazett's correction) intervals averaged across all 12 surface ECG leads estimated by an electronic caliper were manually checked at 6-weeks and 6-months post CRT during RV pacing to allow comparison with ARI data. The trend of changes in QTc intervals reflected regional ARI measured in the responders and the non-responders. At 6 weeks, the QTc was 554±52ms (responders), 543±50ms (non-responders); and at 6 months 536±54ms, 558±49ms, respectively. The changes were Δ -17±14 for responders; and Δ +16±11 for non-responders, $p<0.01$. A weak correlation was observed between Δ ARI and Δ QTc, $r= 0.59$, $p <0.01$.

A similar divergent change was observed in TPS between the two groups with responders showing a decrease in TPS in radial, circumferential and longitudinal strains between 6 weeks and 6 months of CRT and non-responders showing an increase. (See Figure 3 and Table 2). The mean values of LVARI at 6 weeks differed (263±46ms vs. 235±23ms), although not significantly different, p=0.12. The difference in ARI between the responders and the non-responders at the 6 weeks post CRT is reflected in the time to peak strain between the responders and the non-responders. A possible explanation for this perceived difference is the differences (although not statistically significant) in baseline QRS duration between the responders and the non-responders.

Figure 3

Table 2

The relationship between changes in ARI and changes in time to peak strain (TPS)

Although for each of the strain measures (radial, circumferential and longitudinal strain), shortening during CRT was associated with APD shortening and vice-versa, the relationship between ARI local strain and TPS was likely to be non-linear (Spearman correlation coefficient 0.72 radial; 0.70 circumferential; 0.71 longitudinal strain, see Figure 4). Nevertheless whether local strain increased or decreased indicated whether APD shortened or lengthened with a high degree of sensitivity and specificity.

Figure 4

Changes in ARI and QRS duration

The relation between changes in ARI during CRT and baseline QRS duration is shown in Figure 5 (upper panel). Above a QRS duration of 145ms ARI shortened during CRT in all patients whereas patients with a baseline QRS below 145ms showed either ARI shortening or lengthening. Changes in ARI in relation to the effect of biventricular pacing on the QRS duration (i.e. difference in QRS duration during biventricular pacing vs. baseline QRS), are shown in Figure 5 (lower panel). A QRS decrease during biventricular pacing was associated with ARI shortening whereas a QRS increase was associated with either ARI shortening or lengthening.

Figure 5

Discussion

The main findings of our study are:(1) patients with heart failure receiving CRT classified as responders exhibit LV ARI shortening in the late activated region, whereas non-responders show ARI lengthening confirming our previous observations; (2) ARI shortening was associated with local decrease in time to peak radial, circumferential and longitudinal strain, whereas ARI lengthening was associated with an increase in all three strain patterns; (3) non-responders have a worsening of local myocardial strain and prolongation of local ARI; (4) the relationship between changes in ARI and changes in local strain patterns was non-linear; (5) a baseline QRS of 145ms separated patients in whom ARI and local strain decreased (>145ms) from patients in whom ARI and local strain either decreased or increased (<145ms) in response to CRT; (6) a decrease in QRS duration during biventricular pacing compared to baseline was associated with ARI shortening in response to CRT, whereas an increase in QRS duration was associated with either ARI shortening or lengthening.

A consistent finding in experimental models of heart failure is ventricular action potential duration prolongation.[19] In a canine model with LBBB ablation, cells isolated from the LV lateral wall after 6 weeks showed APD prolongation which was attenuated by CRT.[8] In humans several studies using body surface ECG measurements have reported repolarization changes during CRT. Braunschweig and colleagues found an initial increase in QT and JT interval followed by a sustained reduction in a group of responders.[16] Lellouche and colleague compared the peak to end of T wave and corrected QT measurements at the time of CRT implantation and after 1 year, and observed a decrease in responders and an increase in QT dispersion and T wave peak-to-end dispersion in non-responders.[20] We recently reported APD

shortening in responders and APD lengthening in non responders during CRT in patients with heart failure using ARI recordings from the LV epicardial free wall.[11]

While the mechanism underlying reverse electrical remodeling during CRT in heart failure is considered to be multifactorial a general consensus is that LV mechanics play an important role.[6-10] Canine models of myocardial dyssynchrony show APD changes with APD shortening in the early activated low strain regions and APD lengthening in the late activated high strain regions.[21,22] In humans, Kroon et al have recently demonstrated a good correlation between LV depolarization pattern and strain pattern in heart failure patients,[23] and our group has also found a similar correlation in heart failure patients with LBBB.[24] Several studies have investigated the effect of CRT on LV mechanics. Strain patterns have been shown to improve in CRT in responders with lesser changes or worsening in non-responders.[25]

At the present time we are unaware of any previous report on the relationship between APD and regional wall mechanics in humans. In the present study we showed concordance between the change in APD and the change in strain pattern during CRT. However, the relation between delta APD and delta strain was not linear. Such a relationship would be consistent with the interaction of dyssynchronous contraction with the electrophysiology being multifactorial resulting in ion channel remodeling involving stretch activated receptors, gap junctions via connexins, calcium handling, beta adrenergic responsiveness, mitochondrial function, fibrosis and other changes.[6-10]

APD prolongation, particularly in the late activated lateral wall, is a consistent manifestation of heart failure and may contribute to the substrate for ventricular arrhythmias. Changes in all three strain patterns identified whether APD would lengthen or shorten during CRT with a high degree of sensitivity and specificity

(Figure 4). Therefore an increase in regional strain would indicate a likely worsening of APD. If this effect were inhomogeneous it would favor re-entry arrhythmia. The prolongation in ARI observed in the non-responders may provide an explanation for the potential harmful effects of CRT in patients with narrow baseline QRS duration.[26] Conversely, improvement in strain pattern has been shown to be an independent predictor of CRT response in terms of long-term outcome including death and hospitalization.[27]

The trend of changes in QTc intervals appears to reflect that of regional ARI measured in the responders and the non-responders. Our results are in keeping with prior findings that QTc interval shortened amongst the responders to CRT.[20] However the weak association between the ARI and QTc reflects that ARI is a local measure of repolarization unlike the QT interval which is a global measure. Other mechanisms in addition to changes in local strain may contribute to the global electrical remodeling following CRT.

Above a baseline QRS duration of 145ms all patients showed APD shortening during CRT whereas below QRS of 145ms patients showed either shortening or lengthening (Figure 5). These electrophysiological changes lend support to the current recommendation for heart failure patients with baseline QRS ≥150ms to receive CRT. In our data a shortening of QRS during biventricular pacing compared to baseline was associated with APD shortening and a lengthening of QRS was associated with either APD shortening or lengthening. This is in keeping with findings of other studies.[28,29] Bonakdar and colleague also found baseline QRS >145ms to be an independent predictor of CRT response with the best sensitivity and specificity.[29]

Methodological considerations

ARI has been extensively theoretically and experimentally validated as a reliable surrogate for local APD.[30] Unlike other measures of repolarization ARI has the advantage of providing local information in contrast to the QT interval and avoids the proarrhythmic risk of premature stimulation during estimation of refractory periods. Two dimensional speckle tracking echocardiography has been shown to be effective and simple in providing useful insights to the mechanics of myocardial contraction. Based on standard grey scale images, strain defined by percentage change of the myocardial fiber length from its relaxed state in end systole is used to quantify myocardial deformation.[31]. Speckle tracking echocardiography has certain advantages compared with tissue velocity imaging and is an accurate way of indexing the complex ventricular contraction motions with radial, circumferential and longitudinal strain measurements.[32]

Limitations

The study cohort is relatively limited in number, but has sufficient power (>95%) to detect a change in LV remodeling based on the data gathered previously.[11] The device programmer only enables recordings of unipolar electrograms to be made from the distal pole of the LV lead, consequently limiting to single site recordings. It has been shown that increased regional dispersion of repolarization varied between responders and non-responders.[33,34] It would be of interest to see how this regional change related to the global LV repolarization time and dispersion as depending on the extent of the region exhibiting the changes; there might be either pro- or antiarrhythmic effects. We are unable to comment on the initial response because no LV strain measurements were acquired immediately after CRT implant due to clinical constraints of patient

discomfort. Anatomical features such as regional scars may alter local stress / strain relations and influence the remodeling process. The present study however was not designed to assess the influence of pathogenesis on the ARI.

Conclusions

Cardiac resynchronization therapy in heart failure patients with dyssynchronous LV electromechanical activation sequence resulted in LV epicardial APD shortening in CRT responders and APD lengthening in non-responders. Changes in regional ventricular wall mechanics, i.e. radial, circumferential and longitudinal strain patterns predicted local APD shortening or lengthening during CRT. Baseline QRS duration and change in QRS between baseline and biventricular pacing could identify patients showing APD shortening during CRT.

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ZC received British Heart Foundation training research fellowship

Disclosures

None

Figure Captions

Figure 1 Speckle tracking analysis and activation recovery interval (ARI) measurement

Panel A: Two-dimensional gray scale echocardiography with speckle tracking to allow strain assessment. B: The three main directions of strain during myocardial contraction. C: Myocardial strain plotted against time and gated to electrocardiography ECG. D: Illustration of the relation between activation time and repolarization time in ventricular action potential and local unipolar electrogram.

Figure 2 Divergent changes in activation recovery interval ARI between 6-weeks and 6-months post CRT between responders and non-responders.

Figure 3 Changes in time to peak strains (radial, circumferential and longitudinal) between 6-weeks and 6-months post CRT between responders and non-responders

Figure 4 Correlation between changes in activation recovery time (ARI) and changes in time to peak strain (TPS)

r = Spearman's correlation coefficient

Figure 5. Relationship between changes in activation recovery interval ARI and baseline QRS duration and CRT paced QRS duration

Figures

Figure 1

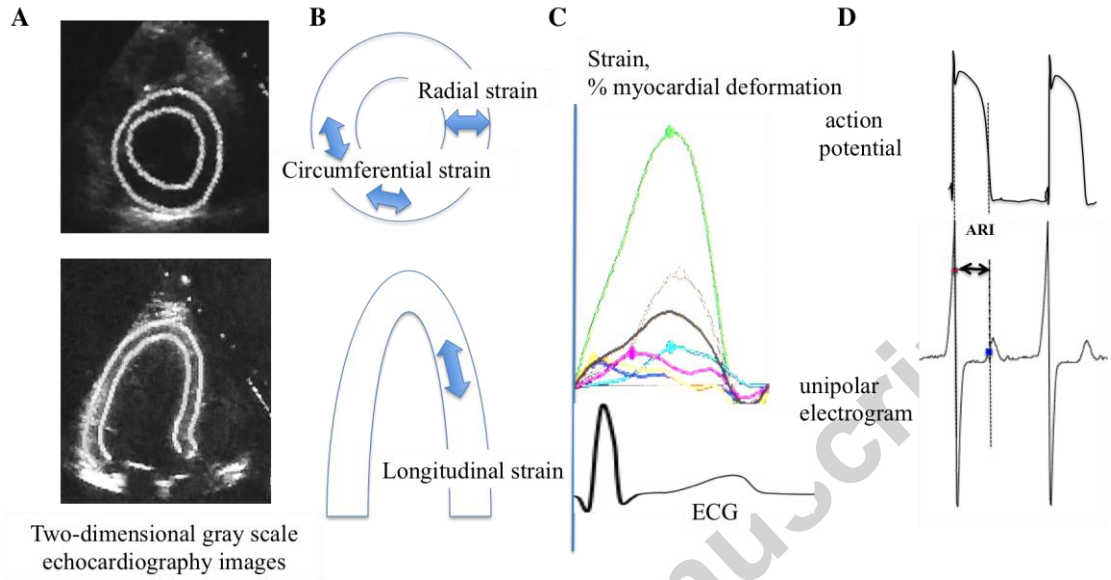


Figure 2

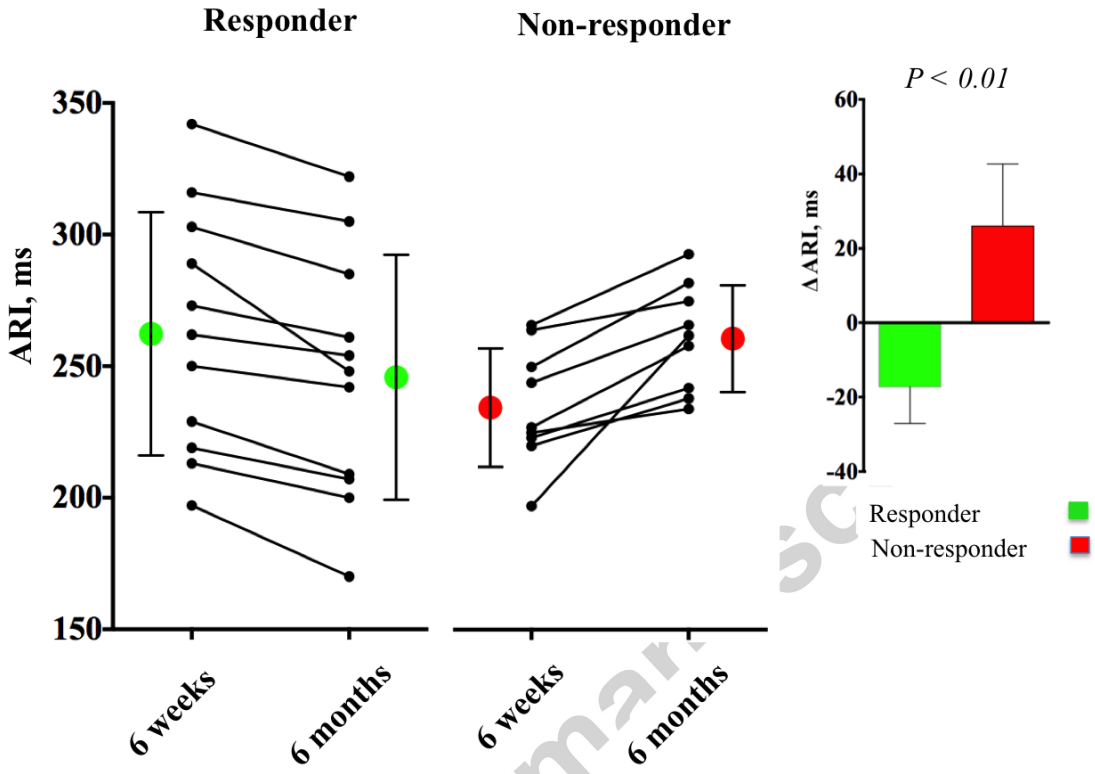


Figure 3

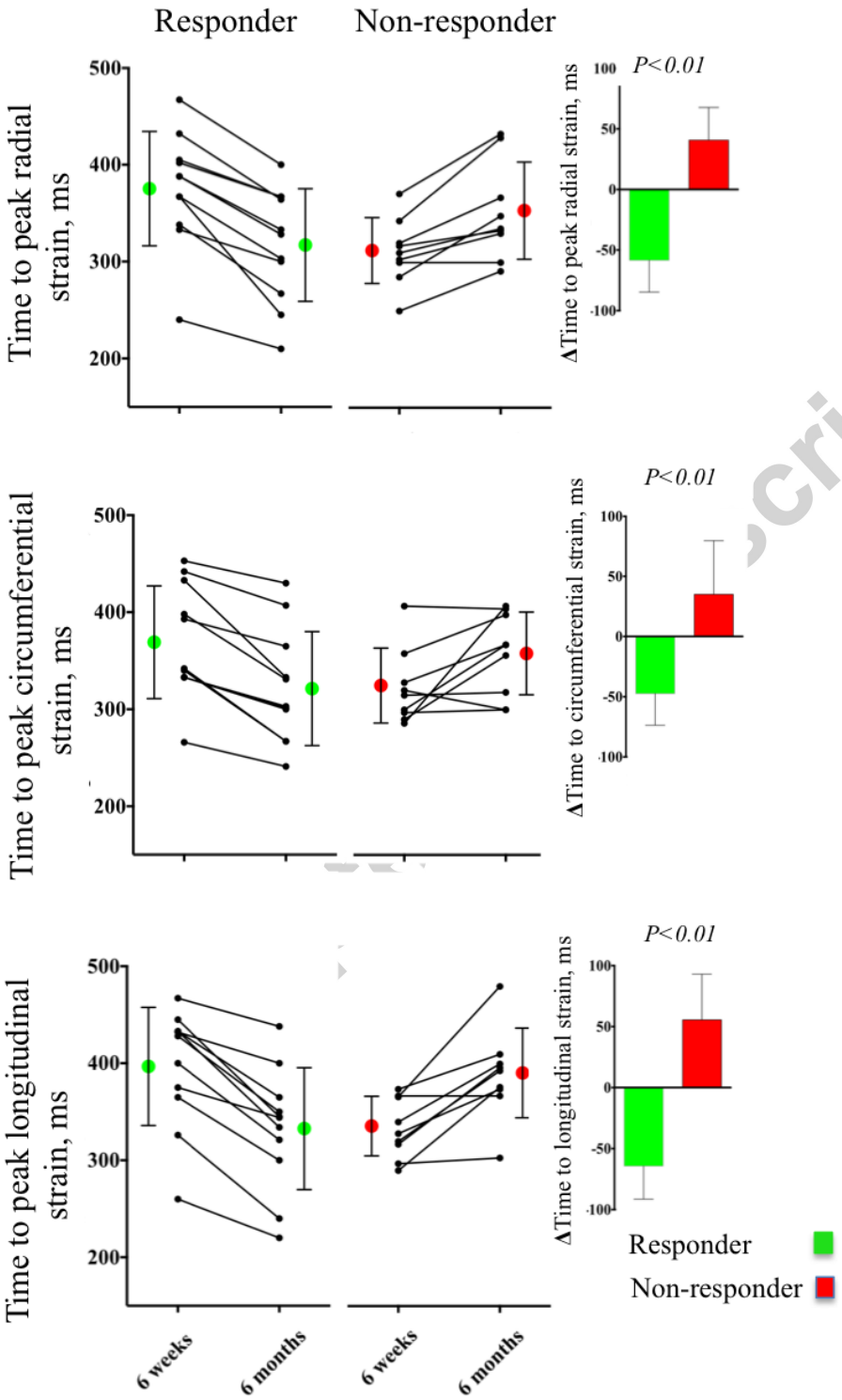
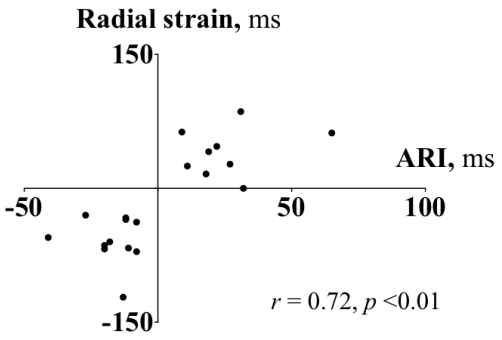
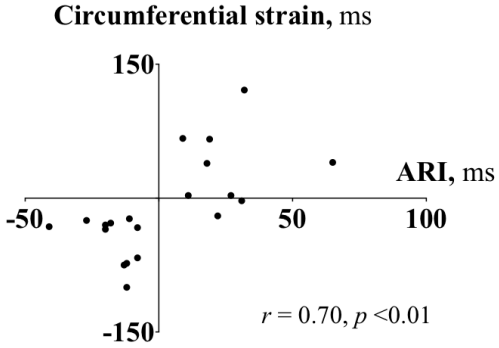

Responder
Non-responder
Time to peak radial strain, ms
ΔTime to peak radial strain, ms
P<0.01
Time to peak circumferential strain, ms
ΔTime to circumferential strain, ms
P<0.01
Time to peak longitudinal strain, ms
ΔTime to longitudinal strain, ms
P<0.01
Responder
Non-responder
6 weeks
6 months
6 weeks
6 months

Figure 4



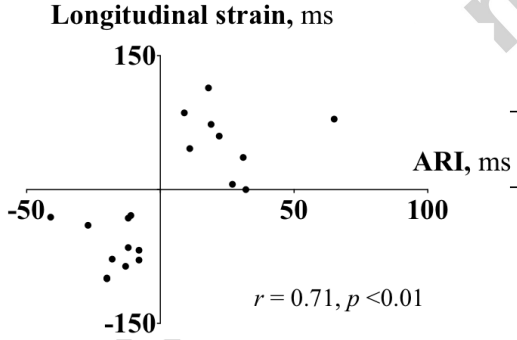
		ARI prolongation	
		No	Yes
TPS (Radial) prolongation	Yes	0	8
	No	11	1

Sensitivity:89% Specificity:100%



		ARI prolongation	
		No	Yes
TPS (Circumferential) prolongation	Yes	0	7
	No	11	2

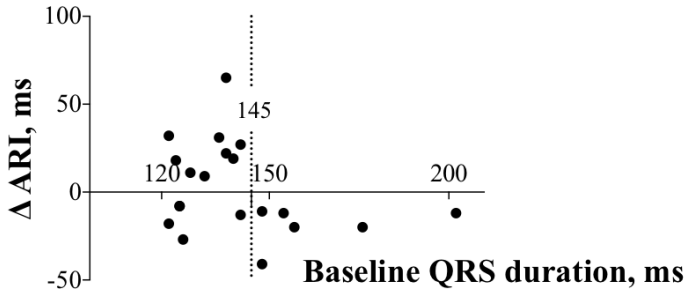
Sensitivity:78% Specificity:100%

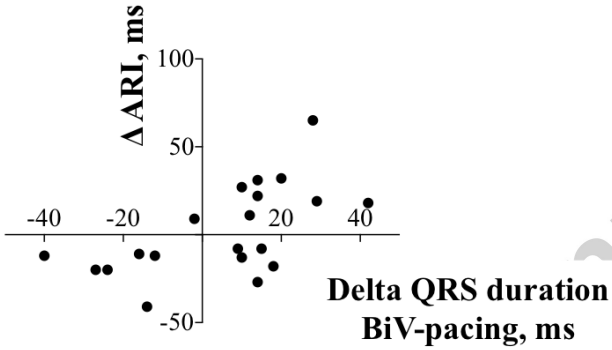


		ARI prolongation	
		No	Yes
TPS (Longitudinal) prolongation	Yes	0	8
	No	11	1

Sensitivity:89% Specificity:100%

Figure 5





Tables

Table 1. Clinical and LV functional response at 6 months

	Responders	Non-responders	*P*
Patient, n	11	9	
NYHA Class	2±1	3±0	*P=0.01*
Minnesota heart failure score	27±15	45±23	*P<0.01*
Δ LVEF, %	+13±7	+1±6	*P<0.01*
Δ LVESV, %	-37±15	+8±23	*P<0.01*

Table 2. Activation recovery intervals (ARI) and time to peak strains (TPS) in responder and non-responder groups

Time, ms	Responders n = 11		Non-responders n = 9		p
6-week ARI,	263±46		235±23		
		Δ -17±10		Δ +26±17	<0.01
6-month ARI,	246±47		261±20		
6-week TPS radial,	375±59		311±34		
		Δ -58±26		Δ +41±27	<0.01
6-month TPS radial,	317±58		352±50		
6-week TPS circumferential	370±58		322±39		
		Δ -47±26		Δ +35±25	<0.01
6-month TPS circumferential	322±59		357±43		
6-week TPS longitudinal	397±61		333±31		
		Δ -64±27		Δ +56±37	<0.01
6-month TPS longitudinal	332±63		389±46		

Reference:

1. Linde C, Abraham WT, Gold MR, et al.: REVERSE (REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction) Study Group: Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. J Am Coll Cardiol 2008;52:1834-1843.

2. Moss AJ, Hall WJ, Cannom DS, et al.: Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med 2009;361:1329-1338.

3. Tang ASL, Wells GA, Talajic M, et al.: Cardiac-resynchronization therapy for mild-to-moderate heart failure. N Engl J Med 2010;363:2385-2395.

4. Cleland JGF, Daubert J-C, Erdmann E, et al.: Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators: The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539-1549.

5. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM: Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140-2150.

6. Prinzen FW, Vernooy K, Auricchio A: Cardiac resynchronization therapy: state-of-the-art of current applications, guidelines, ongoing trials, and areas of controversy. Circulation 2013;128:2407-2418.

7. Abraham WT, Hayes DL: Cardiac resynchronization therapy for heart failure. Circulation 2003;108:2596-2603.

8. Aiba T, Hesketh GG, Barth AS, Liu T, Daya S, Chakir K, Dimaano VL, Abraham TP, O'Rourke B, Akar FG, Kass DA, Tomaselli GF: Electrophysiological consequences of dyssynchronous heart failure and its restoration by resynchronization therapy. Circulation 2009;119:1220-1230.

9. Cho H, Barth AS, Tomaselli GF: Basic science of cardiac resynchronization therapy: molecular and electrophysiological mechanisms. Circ Arrhythm Electrophysiol 2012;5:594-603.

10. Kirk JA, Kass DA: Electromechanical dyssynchrony and resynchronization of the failing heart. Circ Res 2013;113:765-776.

11. Chen Z, Hanson B, Sohal M, Sammut E, Child N, Shetty A, Boucher R, Bostock J, Gill J, Carr-White G, Rinaldi CA, Taggart P: Left ventricular epicardial electrograms show divergent changes in action potential duration in responders and nonresponders to cardiac resynchronization therapy. Circ

Arrhythm Electrophysiol 2013;6:265-271.

12. Bleeker GB, Mollema SA, Holman ER, Van de Veire N, Ypenburg C, Boersma E, van der Wall EE, Schalij MJ, Bax JJ: Left ventricular resynchronization is mandatory for response to cardiac resynchronization therapy: analysis in patients with echocardiographic evidence of left ventricular dyssynchrony at baseline. Circulation 2007;116:1440-1448.

13. Chatterjee NA, Roka A, Lubitz SA, Gold MR, Daubert C, Linde C, Steffel J, Singh JP, Mela T: Reduced appropriate implantable cardioverter-defibrillator therapy after cardiac resynchronization therapy-induced left ventricular function recovery: a meta-analysis and systematic review. Eur Heart J 2015;36:2780-9

14. Haugaa KH, Marek JJ, Ahmed M, Ryo K: Mechanical dyssynchrony after cardiac resynchronization therapy for severely symptomatic heart failure is associated with risk for ventricular arrhythmias. Journal of the American … 2014;27:872-9

15. Hasselberg NE, Haugaa KH, Bernard A, Ribe MP, Kongsgaard E, Donal E, Edvardsen T: Left ventricular markers of mortality and ventricular arrhythmias in heart failure patients with cardiac resynchronization therapy. Eur Heart J Cardiovasc Imaging 2016;17:343-50

16. Braunschweig F, Pfizenmayer H, Rubulis A, Schoels W, Linde C, Bergfeldt L: Transient repolarization instability following the initiation of cardiac resynchronization therapy. Europace 2011;13:1327-1334.

17. Franz MR, Swerdlow CD, Liem LB, Schaefer J: Cycle length dependence of human action potential duration in vivo. Effects of single extrastimuli, sudden sustained rate acceleration and deceleration, and different steady-state frequencies. J Clin Invest 1988;82:972-979.

18. Bueno-Orovio A, Hanson BM, Gill JS, Taggart P, Rodriguez B: Slow adaptation of ventricular repolarization as a cause of arrhythmia? Methods Inf Med 2014;53:320-323.

19. Aiba T, Tomaselli GF: Electrical remodeling in the failing heart. Curr Opin Cardiol 2010;25:29-36.

20. Lellouche N, De Diego C, Boyle NG, Wiener I, Akopyan G, Child JS, Shivkumar K: Relationship between mechanical and electrical remodelling in patients with cardiac resynchronization implanted defibrillators. Europace 2011;13:1180-1187.

21. Aiba T, Tomaselli G: Electrical remodeling in dyssynchrony and resynchronization. J Cardiovasc Transl Res 2012;5:170-179.

22. Jeyaraj D, Ashwath M, Rosenbaum DS: Pathophysiology and clinical implications of cardiac memory. Pacing Clin Electrophysiol 2009 Edition. 2010;33:346-352.

23. Kroon W, Lumens J, Potse M, Suerder D, Klersy C, Regoli F, Murzilli R, Moccetti T, Delhaas T, Krause R, Prinzen FW, Auricchio A: In vivo electromechanical assessment of heart failure patients with prolonged QRS duration. Heart Rhythm 2015;12:1259-1267.

24. Sohal M, Shetty A, Duckett S, Chen Z, Sammut E, Amraoui S, Carr-White G, Razavi R, Rinaldi CA: Noninvasive assessment of LV contraction patterns using CMR to identify responders to CRT. JACC Cardiovasc Imaging 2013;6:864-873.

25. Bernard A, Donal E, Leclercq C, Schnell F, Fournet M, Reynaud A, Thébault C, Mabo P, Daubert J-C, Hernandez A: Impact of Cardiac Resynchronization Therapy on Left Ventricular Mechanics: Understanding the Response through a New Quantitative Approach Based on Longitudinal Strain Integrals. J Am Soc Echocardiogr 2015;28:700-708.

26. Ruschitzka F, Abraham WT, Singh JP, et al.: Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. N Engl J Med 2013; 369:1395-1405.

27. Khan FZ, Virdee MS, Palmer CR, Pugh PJ, O'Halloran D, Elsik M, Read PA, Begley D, Fynn SP, Dutka DP: Targeted left ventricular lead placement to guide cardiac resynchronization therapy: the TARGET study: a randomized, controlled trial. J Am Coll Cardiol 2012;59:1509-1518.

28. Serdoz LV, Daleffe E, Merlo M, Zecchin M, Barbati G, Pecora D, Pinamonti B, Fantoni C, Lupo P, Di Lenarda A, Sinagra G, Cappato R: Predictors for restoration of normal left ventricular function in response to cardiac resynchronization therapy measured at time of implantation. Am J Cardiol 2011;108:75-80.

29. Bonakdar HR, Jorat MV, Fazelifar AF, Alizadeh A, Givtaj N, Sameie N, Sadeghpour A, Haghjoo M: Prediction of response to cardiac resynchronization therapy using simple electrocardiographic and echocardiographic tools. Europace 2009;11:1330-1337.

30. Potse M, Vinet A, Opthof T, Coronel R: Validation of a simple model for the morphology of the T wave in unipolar electrograms. Am J Physiol Heart Circ Physiol 2009;297:H792-H801.

31. Park S-J, Miyazaki C, Bruce CJ, Ommen S, Miller FA, Oh JK: Left ventricular torsion by two-dimensional speckle tracking echocardiography in patients with diastolic dysfunction and normal ejection fraction. J Am Soc Echocardiogr 2008;21:1129-1137.

32. Altiok E, Neizel M, Tiemann S, Krass V, Kuhr K, Becker M, Zwicker C, Koos R, Lehmacher W, Kelm M, Marx N, Hoffmann R: Quantitative analysis of endocardial and epicardial left ventricular myocardial deformation-comparison of strain-encoded cardiac magnetic resonance imaging with two-dimensional speckle-tracking echocardiography. J Am Soc Echocardiogr 2012;25:1179-1188.

33. Jeyaraj D, Wilson LD, Zhong J, Flask C, Saffitz JE, Deschenes I, Yu X, Rosenbaum DS: Mechanoelectrical feedback as novel mechanism of cardiac electrical remodeling. Circulation 2007 Edition. 2007;115:3145-3155.

34. Suzuki A, Shiga T, Nakai K, Futagawa K, Matsuyama Y, Shoda M, Kasanuki H, Hagiwara N: Interlead difference between T-peak to T-end intervals in resynchronization patients with an implantable cardioverter-defibrillator. J Electrocardiol 2010;43:706-712.