Left atrial function, a new predictor of response to cardiac resynchronization therapy?

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Running Title: Left atrium and resynchronization

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ABSTRACT:

Background: Cardiac resynchronization therapy (CRT) improves left ventricular (LV) function and induces LV remodeling, and it is an established therapy for advanced heart failure with prolonged QRS duration. One third of patients will not benefit from this invasive therapy.

Objective: We sought to evaluate whether left atrial (LA) strain imaging (ε) parameters could help in predicting the response in terms of LV reverse remodeling after CRT.

Methods: A total of 79 patients who underwent CRT were evaluated with echography before implantation. LA function and LV function were assessed with M-mode, two-dimensional echocardiography, Doppler, tissue Doppler velocity and ε. LV reverse remodeling was defined as a reduction in LV end-systolic volume of >15%.

Results : At 6 months, 54 (68%) patients were responders to CRT. In multivariable logistic regression, LA systolic peak of strain rate (SRA) (OR = 10.5; 95% CI=1.76-62.1, p=0.01), left bundle branch block (OR=6.8, 95% CI = 1.06-43.9, p=0.04), ischemic cardiomyopathy (OR=3.93, 95% CI=1.07-14.4, p=0.04) and LV pre-ejection index (OR=1.03, 95% CI=1.01-1.05, p=0.01) were associated with CRT response. With an SRA cut-off of -0.75%, the negative predictive value for predicting CRT response was 0.62.

Conclusion: The present study demonstrated that it could be ~~enormously~~ relevant to assess LA function before CRT. SRA appeared to be a good predictor of CRT response. Integrating this LA function analysis into the multivariable assessment of patient candidates for CRT should be considered.

Key words: cardiac resynchronization therapy, left atrial function, strain imaging, echocardiography

List of the abbreviations:

CRT: cardiac resynchronization therapy

LA: left atrial

LV: left ventricular

EF: ejection fraction

AV: atrio ventricular

DFT: diastolic filling time

V: volume

LVPEI: LV pre-ejection interval

IVMD: inter-ventricular mechanical delay

Introduction

Echocardiography plays an important role in patient assessment before cardiac resynchronization therapy (CRT), and it can monitor many of the mechanical effects of CRT in heart failure patients [1 2 3]. Encouraged by the highly variable individual response observed in the major CRT trials, echocardiography-based measurements of mechanical dyssynchrony have been extensively investigated, with the aim of improving the prediction of response to CRT [2 4 5 6 7]. There has been no consensus on mechanical dyssynchrony analysis before CRT implantation because larger studies have been somewhat disappointing[1 8 9]. According to the current literature, it seems that one can still hope to predict the response to CRT with mechanical dyssynchrony analysis, but the negative predictive value of all of the proposed approaches remains low[10].

Apart from mechanical dyssynchrony, other morphologic parameters have been tested to predict CRT response. Leyva et al[11] considered left ventricle fibrosis assessed by cardiac magnetic resonance. Damy et al[12] showed the prognostic value of right ventricle function.

There have also been a few studies examining the relationship of the left atrium (LA) with CRT [13] [14]. Until now, diastolic function, with the exception of atrio-ventricular dyssynchrony[15], has not been expected to be reported when assessing a patient before CRT implantation. Nevertheless, the value of LA volume as a strong prognostic marker has largely been demonstrated in many fields, including systolic heart failure[16]. Furthermore, we can easily assess the size of the LA, as well as its function to some extent. Very promising observations have been made in the field of CRT[17], including a study performed in our institution[14], and even more observations have been made in the field of valvular heart disease [18]. Speckle tracking echocardiography is a novel method for angle-independent and objective quantification of myocardial deformation from standard bidimensional datasets; speckle tracking has the advantages of being angle-independent and being weakly affected by reverberations, side lobes and dropout artifacts. Speckle tracking echocardiography has recently evolved, and, by enabling the quantification of longitudinal myocardial LA-deformation dynamics, it was recently proposed as an alternative approach for the estimation of LV filling pressure. In fact, the LA is exposed to the cumulative effects of filling pressures over time and could, therefore, provide a more sensitive and likely more relevant expression of the severity of LV (and heart as a whole) dysfunction than measurement of the characteristics of the left ventricle.

Therefore, we sought to examine the ability of LA function characteristics to predict response to treatment in a typical population of patients referred for CRT.

Methods

Patient population

Between April 2007 and February 2012, consecutive patients scheduled to undergo implantation of CRT systems at the Rennes University medical center were prospectively

included in this study. The goal was to assess the feasibility and value of using LA strain (as a relevant manner for assessing LA function), in terms of predicting LV-reverse remodeling. The inclusion criteria were: 1) New York Heart Association (NYHA) functional class II-IV, despite optimal medical therapy; 2) an LVEF ≤35%; 3) a stable sinus rhythm, 4) a QRS duration ≥120 ms on 12-lead electrocardiography; and 5) no previous pacemaker or cardioverter defibrillator implantation. Patients with atrial fibrillation were excluded. Heart disease was considered ischemic if a 50% stenosis was observed in ≥1 major epicardial coronary artery or if the patient had a history of myocardial infarction or prior coronary revascularization. The patients were followed up at 6 months after implantation of the device. No patients were lost to follow-up, and all of them returned to the laboratory to meet the requirements of the study.

Responders were defined as having a ≥15 % decrease in left ventricular end-systolic volume at the 6-month follow-up, compared with baseline. This measurement was chosen because it was the endpoint chosen in most of the studies in this field [19].

This study was performed in accordance with the principles outlined in the Declaration of Helsinki on research in human subjects and with the procedures of the Rennes University Hospital Medical Ethics Committee (usual care). The study was approved by a national review committee (no. CNIL 0507317b). The patients provided their informed consent.

Transthoracic echocardiography

Each patient was placed in the left lateral decubitus position and was assessed using echocardiography with either the Vivid 7 or Vivid e 9 ultrasound system (GE Medical Systems, Horten, Norway), equipped with 2.5-MHz transducers. LV volume and LA volume (LAV) were quantified according to the recommendations of the American Society of Echocardiography [20]. LAVs were calculated using the apical 4- and 2-chamber area-length

method, and they were subsequently indexed to body surface area (LAV index [LAVI]) as described earlier[21]. Trans-mitral flow (E wave and deceleration time) and mitral annular tissue Doppler (E′ and S′) velocities were measured. The Doppler value recorded was the mean of three beats. All of the measurements were obtained according to recommendations of chamber quantification[20] and diastolic function assessment [22]. Diastolic filling time (DFT)/RR interval ratio was used to characterize atrioventricular (AV) dyssynchrony in the left heart. AV dyssynchrony was defined as DFT/RR <40%[15]. LV pre-ejection interval (LVPEI), and IVMD (inter-ventricular mechanical delay) were used to characterize interventricular dyssynchrony[15].

Left atrial deformation imaging indices

Three consecutive cardiac cycles were recorded and averaged, and the frame rate was set to 60 to 80 frames/sec. The analysis was performed offline using customized software (EchoPAC PC BT12; GE healthcare, Horten, Norway). The LA endocardial border was manually traced on the apical four-chamber view. After manual adjustment of a region of interest covering the full thickness of the myocardium, the software divided the left atrium into six segments and automatically scored the segmental tracking quality. The software rejected segments with inadequate image quality and excluded them from the analysis. Longitudinal strain curves were generated for each of the 6 LA segments in the four chambers. Global peak LA longitudinal strain during ventricular systole (εs) was then measured by averaging the values obtained from the 6 LA segments. The same tracing method was used to calculate the strain rate and to analyze the LA systolic peak of strain rate (SRA) [23]. A cardiologist with a level 3 in echocardiography, who was unaware of the patients' information, analyzed all of the echocardiographic values (figure 1).

Observer variability

Twenty studies were randomly selected for inter-observer and intra-observer variability. Systolic strain and the strain rate from the left atrium apical four-chamber view were re-measured by the same observer and by a second independent observer based on the digital data, using an offline system.

Statistical analysis

Continuous variables are presented as means (SDs) or medians (IQRs) in cases of skewness. Categorical data are summarized as frequencies and percentages. Differences in baseline characteristics between the two groups (responders and non-responders) were analyzed with Student's t-test, the Mann-Whitney test, the Chi-square test or Fisher's exact test, as appropriate. Correlations between variables were determined with Pearson's product moment correlation analysis. Multivariate logistic regression analysis was used to assess relationships between the different variables and CRT response. We included in the multivariable analysis all of the variables with $p < 0.05$ in univariate analysis, after removing correlated variables (Pearson's coefficient > 0.70). Stepwise forward/backward selection was performed according to the Akaike Information Criterion. Optimal cut-off values of LA parameters to predict response to CRT were determined by ROC curve analysis. The optimal cut-off value was defined as that providing maximal accuracy to distinguish between responders and non-responders. A p value < 0.05 was considered statistically significant.

All of the statistical analyses were performed with the software package R (R Foundation for Statistical Computing, Vienna, Austria; URL: http://www.R-project.org/).

Results

Study population and Clinical Status

A total of 79 patients, of 102 consecutive patients (77%), were considered based on the recordings of their echocardiography, providing images allowing for the measurement of εs and SR-A. Their baseline demographic, clinical, echocardiographic characteristics are presented in **table 1**. The disease etiology was ischemic in 25% of the patients. More than 90% of patients were treated with a beta-adrenergic blocker and an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker at the highest tolerated doses. At 6 months, 68 % of the patients were responders to CRT.

Measurement of Reproducibility

For εs, the ICCs were 0.96 and 0.90, respectively, for inter- and intra-observer agreement, and for SRA, the ICCs were 0.83 and 0.78, respectively. The measurements of εs and SRA showed good reproducibility, with intra-observer and inter-observer variations similar to those reported in the literature (**table 2**).[24]

Uni and multi-variable analysis

The differences between basal clinical and echocardiographic parameters for the population and according to CRT response are shown in **table 1**. All of the parameters with a $p < 0.05$ in univariate logistic regression were entered into a multivariable logistic regression analysis. εs and SRA were strongly correlated (Pearson's $r = 0.81$) and could not be analyzed together, so two multivariate logistic regression analyses were performed. The results are shown in **table 3**. In multivariate analysis, the following were associated with CRT response: SRA (OR = 4.7, $p = 0.02$), LBBB (OR = 4.5, $p = 0.05$), non-ischemic cardiomyopathy (OR = 3.73, $p = 0.04$), LVPEI (OR = 1.02, $p = 0.014$) and εs (OR=1.12, p=0.04).

ROC analysis

The ROC for SRA is shown in Figure 2

. **Table 4** shows the accuracy of testing according to different cut-off value. The best accuracy (0.77) was obtained with an SRA value of -0.75%. The best negative predictive value (NPV) was 0.62 in our population (64% of responders) and was obtained with an SRA value of -0.75%. The best Predictive Positive Value (PPV) in our population is 0.89 and was obtained with a SRA value of -1%. Regarding LVPEI, the best cut-off in our population was 125 ms (140 ms in the literature [15]). With this value, the accuracy was 0.76, and the PPV and NPV were, respectively, 0.86 and 0.60. If we associated LVPEI > 125 ms with SRA<0.75%, the PPV to predict CRT was 0.97, the NPV was then 0.53, and the accuracy was 0.72.

Discussion

The present study demonstrated that it could be quite relevant to assess LA function and, in particular, to consider LA strain data for predicting CRT response and non-response.

LA has been proposed as being analogous in heart conditions to HbA1c in diabetes. . Nevertheless, very few investigations have been published that have examined the promising role of LA strain imaging in better understanding and perhaps in predicting the response or non-response to CRT. D'Andrea et al[13] reported that LA strain could be measured in candidates for CRT. We previously observed significant reverse remodeling in LA functional, structural, and anatomic characteristics after successful CRT. LA reverse remodeling was correlated with baseline LA volume[14]. Yu et al [17] showed that responders to CRT had improvements in contraction velocity in both the left and right atria, as well as improvement in LA reverse remodeling with a reduction in the LA size. LA reverse remodeling was also more frequent in patients with LV reverse remodeling [14].

The LA has multiple functions: it acts as a reservoir for blood during ventricular systole (atrial compliance), as a conduit for the passage of blood from the pulmonary veins to the left ventricle in early diastole (passive emptying) and as a contractile chamber to augment left ventricular filling in late diastole (active atrial contraction). LA size[16 23] and function[25] have been used as prognostic markers for adverse cardiovascular events in numerous clinical settings.

Nevertheless, there is currently no accepted 'gold standard' for evaluating LA function, despite very promising studies. ε and SR techniques have enabled the evaluation of atrial function throughout the cardiac cycle, thereby facilitating the measurement of phasic atrial function. εS and SRA serve as measurements of LA compliance during the reservoir phase, with early diastolic SR a measurement of passive emptying during the conduit phase and late diastolic SR a measurement of active atrial contraction ()[23]. These parameters seem correlated with, or at least influenced by, atrial fibrosis. Kuppahaly et al [26] showed that there were correlations of LA fibrosis detected by delayed-enhancement MRI with LA ε and SR. Cameli et al [27] showed, in patients with severe MR, a close, negative correlation between measured εS and histological LA fibrosis grade. In a previous study, atrial fibrosis was strongly associated with prognosis in heart failure [28]. We could hypothesize that severe cardiomyopathy, with a fibrotic and not a deforming atrium, is not an adequate candidate for CRT. SRA and εS, as surrogate markers for atrial fibrosis, could help to define this group of cardiomyopathies, which would be too greatly remodeled to expect any reverse remodeling with any type of treatment. That remains a hypothesis and further prospective multi-center validation studies are required. The respective value of strain and strain rate is requiring the transfer of our monocentric observations to a prospective multicenter validation.

Of course, LA function would have to be considered, in addition to other critical parameters.

First, LBBB was a strong predictor of response to CRT in our study. The enrollment of

patients occurred between 2010 and 2011, and the guidelines were more focused on QRS width than on QRS morphology, as they now are [9]. This focus emphasized the importance of morphology over width. Ischemic cardiomyopathy has a lower response to CRT, as shown earlier [19]. Additionally, the original goal of CRT was mitigation of mechanical dyssynchrony between the right and left ventricles, with a view toward improving hemodynamic function. Contraction of some segments might be so delayed that they end past the onset of ventricular filling and after the end of ejection, causing intra-ventricular asynchrony due to the coexistence of systole and diastole. LVPEI was used and validated to assess this mechanical dyssynchrony [15]. In our study, in multivariable analysis, LVPEI was one of the parameters that predicted response to CRT. It is a simple index and one that has not been discredited in prospective trials [1]. The present study focused on the value of LA function and particularly LA strain parameters for understanding the response to CRT.

Limitations

This was a mechanistic study that had as its only aim providing new knowledge about the mechanisms implicated in the response to CRT. We focused on the LA because LA strain and ε seemed perhaps more predictive of the response to CRT than the usual LV parameters that have been extensively studied previously. We must acknowledge that we only focused on the LA and not on the two atrial functions or on synchronicity. The far location of the atrium, the reduced signal-to-noise ratio, the thin atrial wall and the presence of the appendage and pulmonary veins make strain imaging of left atrium more difficult and time consuming than for the LV [23]. Nevertheless, with dedicated attention (focusing on the atrium) and with the improvements in software proposed year after year, the application of speckle tracking in

daily clinical routine is likely not a dream but almost a reality, provided its incremental value is confirmed in further studies.

Conclusion

The present study demonstrated that it could be relevant to assess LA function before CRT. SRA appeared to be a good predictor of CRT response. Integrating this LA function analysis into the multivariable assessment of patients who are candidates for CRT should be considered.

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Clinical perspectives:

Cardiac resynchronization therapy (CRT) improves left ventricular (LV) function and induces LV remodeling, and it is an established therapy for advanced heart failure with prolonged QRS duration. One third of patients will not benefit from this invasive therapy. The LA is exposed to the cumulative effects of filling pressures over time and could, therefore, provide a more sensitive and likely relevant expression of the severity of disease and of the risk of non-response to a treatment supposed to reverse the remodeling. LA function could be robustly analyzed using speckle tracking and strain data. The present study demonstrated that it could be relevant to assess LA function before CRT.

Table 1: Baseline Characteristics of Patients

Variable	All (n=79)	CRT non-responders (n=25)	CRT responders (n=54)	p
Men	54 (68.4%)	20 (80.0%)	34 (63.0)	0.97
Age (years old)	63.66 (10.59)	66.56 (10.17)	62.31 (10.60)	0.1
Ischemic cardiomyopathy	25 (31.6%)	15 (60.0%)	10 (18.5%)	<0.01
Heart rate (beats/min)	66.51 (13.03)	64.72 (10.99)	67.33 (13.89)	0.41
LBBB	66 (83.5%)	16 (64.0%)	50 (92.6%)	<0.01
QRS (ms)	162.4 (20)	158.8 (30)	163.6 (27.5)	0.086
NYHA (%):				0.70
2	16 (23.2%)	5 (21.7%)	11 (23.9%)	
3	53 (76.8%)	18 (78.3%)	35 (76.1%)	
6 m WT (m)	414 (103)	423 (73.5)	414 (121.5)	0.68
Septal flash	58 (73.4%)	13 (52.0%)	45 (83.3%)	<0.01
LV EF	0.27 (0.10)	0.30 (0.12)	0.27 (0.9)	0.40
GLS (%)	7.54 (2.58)	7.47 (3.13)	7.58 (2.31)	0.86
LV ED diameter (mm)	67 (8)	69 (8)	66 (8)	0.1
IV-delay (ms)	43 (24)	30 (19)	49 (24)	0.001
LVPEI (ms)	136 (34)	117 (30)	145 (32)	<0.001
Ratio diastole/RR (%)	0.44 (0.11)	0.49 (0.09)	0.42 (0.11)	0.01
Ratio E/A	0.89 (0.74)	1.29 (0.89)	0.76 (0.46)	<0.01
Ratio E/Ea	12.62 (6.56)	14.70 (8.07)	12.12 (5.82)	0.03
LA Vi (ml)	41 (19)	46 (13)	38 (18)	0.04
TAPSE (mm)	18 (4)	17 (3)	19 (4)	0.10
SRA (s-1)	-1.00 (0.84)	-0.65 (0.35)	-1.19 (0.76)	<0.001
εs (%)	13.10 (9.75)	10.30 (5.9)	14.60 (9.42)	<0.01
NT-ProBNP (pg/ml)	1238 (1882)	1993 (1447)	974 (1988)	0.08

LBBB: Left Bundle Branch Block – 6m WT: 6 Minute Walking Test - LV EF: Left Ventricle Ejection Fraction – GLS: Global Longitudinal Strain – LA Vi: Left Atrium Volume Index – TAPSE: Tricuspid

Annular Plane Systolic Excursion – SRA: LA Systolic Peak of Strain Rate – εs: LA global Longitudinal Strain

Table 2: Inter- and Intra-observer Reproducibility of LA Strain and Strain Rate

Variable	Interobserver			Intraobserver		
	Relative difference	COV	ICC	Relative difference	COV	ICC
Es	0.17 +/- 1.02	10.40%	0.98 (0.94 - 0.99)	-0.14 +/- 1.30	13.30%	0.95 (0.87 - 0.98)
SRA	0.12 +/- 0.14	20.70%	0.83 (0.24 -0.95)	-0.005 +/- 0.12	16.50%	0.78 (0.33 - 0.92)

COV: Coefficient of Variation – ICC: Intra-Class Coefficient – SRA: LA Systolic Peak of Strain Rate – εs: LA global Longitudinal Strain

Table 3: Logistic Regression Analysis

Variable	Univariable logistic regression		Multivariable logistic regression	
	OR	P	OR	p
Male sex	0.42 (0.14 - 1.31)	0.14	0.74 (0.12 - 4.4)	0.74
Age (years old)	0.96 (0.92 - 1.01)	0.1	0.95 (0.87 - 1.02)	0.16
Ischemic Cardiomyopathy	6.6 (2.3 - 18.9)	0.0005	3.73 (1.01 - 13.8)	0.04
Heart Rate (beats/min)	1.02 (0.98 - 1.05)	0.41		
LBBB	7.03 (1.9 - 25.9)	0.003	4.5 (0.87 – 22.9)	0.05
QRS (ms)	1.02 (0.99 - 1.05)	0.22		
NYHA (%):	0.61 (0.16 - 2.34)	0.47		
6 m WT (m)	1 (0.99 - 1.01)	0.92		
Septal Flash	4.62 (1.6 - 13.3)	0.005	2.1 (0.5 - 8.7)	0.31
LV EF	0.06 (0.001 - 87.5)	0.45		
GLS (%)	1.02 (0.84 - 1.23)	0.86		
LV EDD (mm)	0.95 (0.90 - 1.01)	0.11		
IV-Delay (ms)	1.04 (1.01 - 1.07)	0.002		
LVPEI (ms)	1.03 (1.01 - 1.05)	0.001	1.02 (1.0 - 1.05)	0.04
Ratio Diastole/RR (%)	0.0016 (0.001 - 0.243)	0.01	0.06 (0.001 - 23.5)	0.35
Ratio E/A	0.67 (0.42 - 1.07)	0.09		
Ratio E/Ea	0.94 (0.87 - 1.01)	0.09		
LA Vi (ml)	0.98 (0.95 - 1.01)	0.20		
TAPSE (mm)	1.11 (0.97 - 1.27)	0.11		
SRA (s-1)	7.19 (2.14 - 24.1)	0.001	4.7 (1.26 - 17.8)	0.02
εs (%)	1.14 (1.04 - 1.26)	0.007	1.12 (1 - 1.24)	0.04*
NT-ProBNP (pg/ml)	1 (1 - 1)	0.6		

LBBB: Left Bundle Branch Block – 6m WT: 6 Minute Walking Test - LV EF: Left Ventricle Ejection Fraction – GLS: Global Longitudinal Strain – LA Vi: Left Atrium Volume Index – TAPSE: Tricuspid Annular Plane Systolic Excursion – SR_A: LA Systolic Peak of Strain Rate – εs: LA Global Longitudinal Strain

*: This result came from a second multivariate model in which SR_A and εs were correlated ($r > 0.7$).

Table 4: SRA and LVPEI Characteristics to Predict CRT Response

Variable	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
SRA < -0.75%	0.80	0..2	0.86	0.62	0.77
SRA < -1%	0.63	0.84	0.89	0.51	0.70
LVPEI > 125 ms	0.78	0.72	0.86	0.60	0.76
LVPEI >140 ms	0.56	0.80	0.86	0.46	0.63
SRA< -0.75% & LVPEI > 125 ms	0.61	0.96	0.97	0.53	0.72

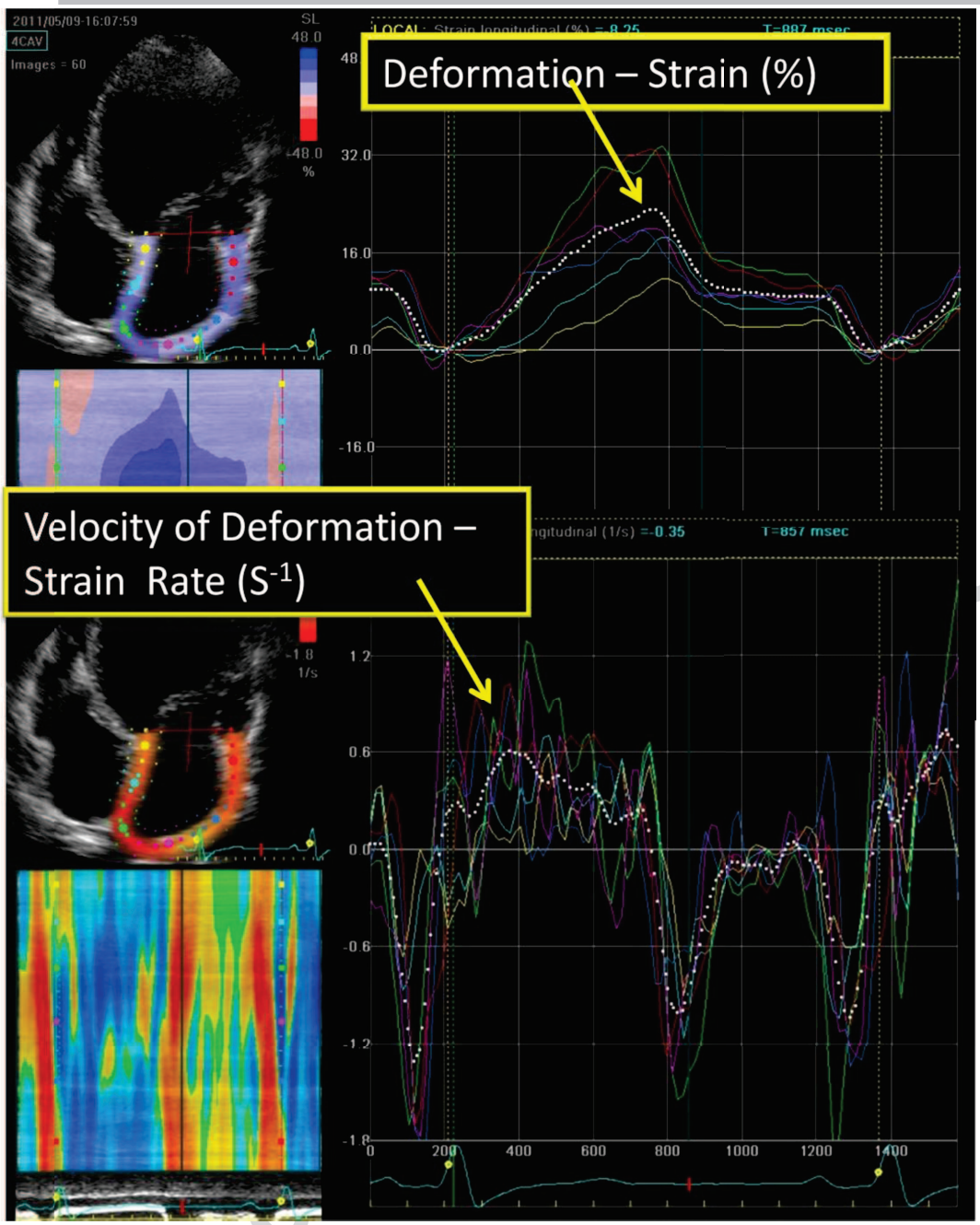
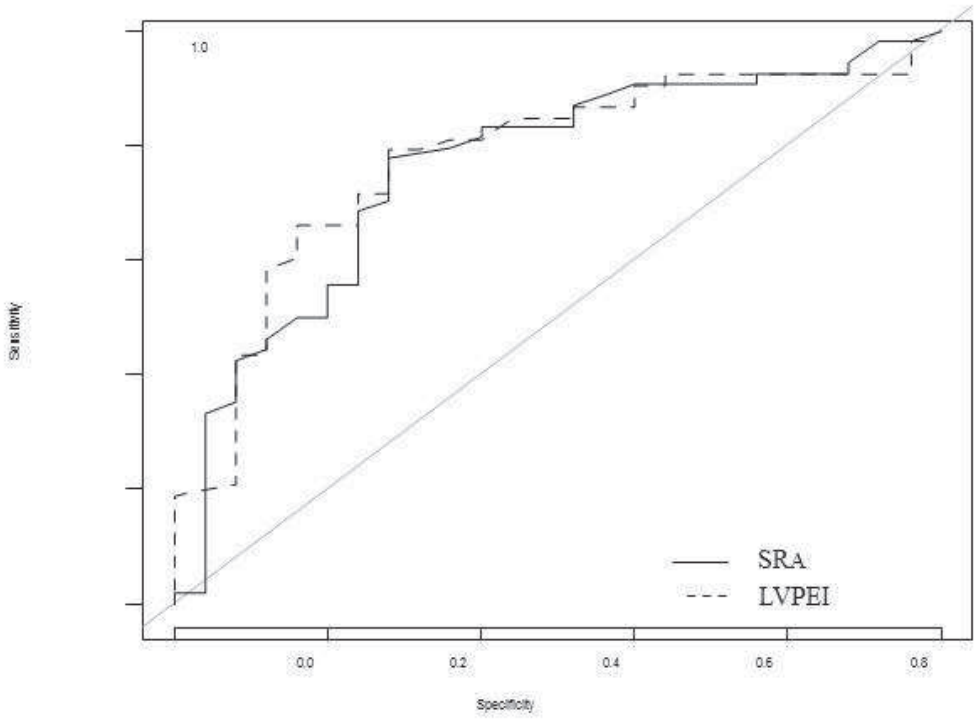


Figure 1: example of left atrial strain and strain rate acquisitions



Variable	AUC	IC 95%
SRA	0,78	0,66 – 0,89
LVPEI	0,76	0,65 – 0,88

Figure 2: ROC Curve for LVPEI (Left) and SRA and Response to Cardiac Resynchronization Therapy at 6 Months