Multimodality imaging to guide cardiac interventional procedures

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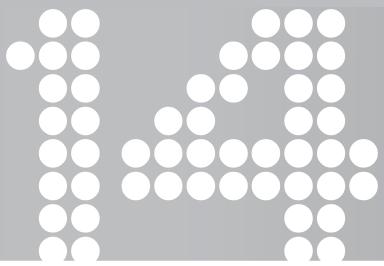

Speckle-tracking radial strain reveals left ventricular dyssynchrony in patients with permanent right ventricular pacing

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ABSTRACT

Background: Recent studies have shown detrimental effects of RV pacing, possibly related to the induction of LV dyssynchrony.

Objectives: Speckle-tracking strain analysis was used to assess the effects of permanent right ventricular (RV) pacing on the heterogeneity in timing of regional wall strain and left ventricular (LV) dyssynchrony.

Methods: Fifty-eight patients treated with His bundle ablation and pacemaker implantation were studied. To assess the effect of RV pacing on time-to-peak radial strain of different LV segments, speckle-tracking analysis was applied to standard LV short-axis images. In addition, NYHA functional class, LV volumes and systolic function were assessed at baseline and after long-term RV pacing.

Results: At baseline, similar time-to-peak strain for the 6 segments was observed (mean 371 ± 114 ms). In contrast, after a mean of 3.8 ± 2.0 years of RV pacing, there was a marked heterogeneity in time-to-peak strain of the 6 segments. In 33 patients (57%) LV dyssynchrony, represented by a time difference ≥130 ms between the time-to-peak strain of the (antero)septal and the posterolateral segments, was present. In these patients, a deterioration of LV systolic function and NYHA class was observed. In 11 patients 'upgrade' of the conventional pacemaker to a biventricular pacemaker resulted in partial reversal of the detrimental effects of RV pacing.

Conclusions: Speckle-tracking analysis revealed that permanent RV pacing induced heterogeneity in time-to-peak strain, resulting in LV dyssynchrony in 57% of patients, associated with deterioration of LV systolic function and NYHA class. Biventricular pacing may reverse these adverse effects of RV pacing.

INTRODUCTION

Cardiac pacing is the only effective treatment in patients with symptomatic sinus node dysfunction or atrioventricular block. In order to maintain atrioventricular synchrony, dual-chamber pacing has been introduced. Surprisingly, large randomized trials have not been able to prove substantial benefit of DDDR pacing over conventional VVIR pacing (1). More importantly, evidence emerges that ventricular pacing should be kept to a minimum (2). Recently, several trials (3-5) have shown that conventional right ventricular (RV) pacing is associated with an increased risk for development of heart failure and death. Furthermore, left ventricular (LV) dilatation (6) and LV dysfunction (7) following RV apical pacing have been demonstrated.

Currently, little data on the exact cause of the deleterious effects of RV pacing exist. Few animal studies have been performed on the effect of the abnormal ventricular activation pattern on regional wall strain (8-10). In a recent study, tissue Doppler imaging was used to demonstrate the possible relation between LV dyssynchrony and the detrimental effects of RV apical pacing (11). Tissue Doppler imaging however is not an ideal method, because with this technique myocardial velocities are assessed, but no information on myocardial strain and active deformation is obtained. We hypothesized that the detrimental effects of RV pacing may be related to the induction of heterogeneity in time-to-peak radial strain of the LV walls, ultimately resulting in LV dyssynchrony. Strain imaging with MRI tagging may be the most accurate technique to assess radial strain and LV dyssynchrony (9); this technique however is technically demanding and is not feasible for patients with pacemakers. However, with the recently introduced speckle tracking analysis applied to standard echocardiograms (12,13), accurate strain imaging using echocardiography has become available.

Therefore, in the current study speckle tracking radial strain was used to evaluate the effect of permanent RV pacing on the heterogeneity in timing of regional strain and LV dyssynchrony. For this purpose, we studied patients with permanent RV apical pacing after His bundle ablation for drug-refractory atrial fibrillation. In addition, the effect of long-term RV pacing on LV systolic function, LV dilatation and functional class was evaluated. Finally, we evaluated whether upgrading RV pacing to biventricular reversed LV dyssynchrony, with an improvement in LV systolic function and functional class.

METHODS

Study sample and study design

Sixty-three patients treated with His bundle ablation and pacemaker implantation were initially screened for the study. All patients had preserved LV systolic function and had no significant valvular disease. Of the 63 patients, 5 patients (8%) were excluded because the echocardiogram image quality was unsuitable for quantitative speckle tracking strain analysis. Eventually, the

study sample comprised 58 patients with drug-refractory, permanent atrial fibrillation. Ten patients were included in a previous study on the effects of permanent RV pacing (11). In all patients a clinical decision to perform a His bundle ablation had been made. Before the His bundle ablation and pacemaker implantation procedure, and after a minimum of 1 year RV pacing, New York Heart Association (NYHA) functional class was assessed and an extensive echocardiographic evaluation was performed. Novel speckle tracking radial strain was used to evaluate the presence of LV dyssynchrony at baseline and after long-term RV pacing. LV systolic function, LV volumes and LV dimensions were assessed at baseline and after long-term RV apical pacing to determine the effect of pacing on global LV function and LV size. Furthermore, the effect of biventricular pacing on LV dyssynchrony and LV function in previously RV paced patients was assessed in 11 patients who received an 'upgrade' of the conventional pacemaker to biventricular pacing because of the presence of LV dyssynchrony and heart failure symptoms.

Ablation and pacemaker implantation

His bundle ablation was performed with a 4 mm quadripolar mapping / ablation catheter (EPT, Boston Scientific, Natick, Massachusetts, USA), accessed through the femoral vein. A temporary pacing electrode was placed in the RV apex for back-up pacing. After the detection of a clear His bundle signal, radiofrequency energy was applied until complete AV-block was achieved. Thereafter the permanent pacemaker was implanted. Pacemaker leads were inserted through the subclavian vein using standard implantation techniques. The RV leads were positioned in the RV apex in all patients. After implantation, pacemakers were routinely programmed to VVIR mode. The day after the procedure an echocardiogram and a standard X-ray was performed to exclude pericardial effusion and lead dislocation.

Echocardiography

All patients underwent echocardiography before the ablation procedure and after long-term permanent RV pacing. Images were recorded with patients in the left lateral decubitus position using a commercially available system (Vingmed Vivid 5 or 7, General Electric-Vingmed, Milwaukee, Wisconsin, USA). Images were obtained using a 3.5-MHz transducer at a depth of 16 cm in the parasternal (long- and short-axis) and apical (2- and 4-chamber) views. Standard two-dimensional images and color Doppler data were digitally stored in cine-loop format.

LV end-diastolic and end-systolic volumes were assessed from the apical 2- and 4-chamber images, and LV ejection fraction was calculated using the biplane Simpson's rule (14). Furthermore, LV end-diastolic and end-systolic diameters were measured from the M-mode recordings derived from the parasternal long-axis images. The severity of mitral regurgitation was graded semi-quantitatively using color-flow Doppler in the conventional parasternal long-axis and apical 4-chamber images (15). Mitral regurgitation was characterized as: minimal = grade 1 (jet area/left atrial area<10%), moderate = grade 2 (jet area/left atrial area 10-20%), moderate-

severe = grade 3 (jet area/left atrial area 20-45%), or severe = grade 4 (jet area/left atrial area >45%) (15).

Strain analysis

Radial strain was assessed on LV short-axis images at the papillary muscle level, using speckle tracking analysis (12,13). Off-line analysis of radial strain was performed on digitally stored images (EchoPac version 6.0.1, General Electric-Vingmed) by 2 independent observers blinded to the clinical and other echocardiographic information. The novel speckle tracking software tracks frame-to-frame movement of natural acoustic markers, or speckles, on standard gray scale images of the myocardium (frame rate varied from 40 to 80 frames/s), as previously described (12,13). In brief, myocardial strain is assessed from temporal differences in the mutual distance of neighboring speckles. The change in length / initial length of the speckle pattern over the cardiac cycle can be used to calculate radial strain, with myocardial thickening represented as positive strain, and myocardial thinning as negative strain. Regional LV strain is assessed using a region of interest that spans the entire LV myocardium throughout the cardiac cycle. The traced endocardium is automatically divided into 6 standard segments: septal, anteroseptal, anterior, lateral, posterior, and inferior, respectively (16).

Time-strain curves for all the 6 segments were constructed. Both peak radial strain values and time from QRS onset to peak radial strain were obtained. Consequently, the location of the earliest and latest activated segments and the heterogeneity in time-to-peak radial strain for the 6 segments were determined. LV dyssynchrony was defined as an interval ≥130 ms for the absolute difference in time-to-peak radial strain for the septal or anteroseptal wall versus the posterior or lateral wall (16). In addition, the time difference between the earliest and latest activated segments was calculated. Furthermore, intra- and interobserver variability for determining the time-to-peak radial strain were evaluated on short-axis images of 15 randomly selected patients. Intraobserver variability for determining the time-to-peak radial strain of all 6 segments was 10 ± 11%, and interobserver variability was 8 ± 7%. The presence or absence of LV dyssynchrony after long-term RV apical pacing was confirmed by tissue Doppler imaging (17).

Upgrading permanent RV pacing to biventricular pacing

Biventricular pacing is able to resynchronize the asynchronous contracting heart. To test the hypothesis that LV dyssynchrony induced by RV apical pacing can be reversed by biventricular pacing, we studied 11 RV paced patients of the study sample who were 'upgraded' to biventricular pacing. In these patients, an upgrade of the conventional pacemaker to a biventricular pacing device (Contak Renewal, Guidant Corporation, St. Paul, Minnesota, USA; or Insync Centry, Medtronic Inc., Minneapolis, Minnesota, USA) was performed because of development of heart failure (NYHA class III or IV) and the presence of LV dyssynchrony. The LV pacing lead was inserted transvenously via the subclavian route. First, a coronary sinus venogram was obtained during occlusion of the coronary sinus using a balloon catheter. Next, the LV pacing lead was

inserted in the coronary sinus with the help of an 8Fr-guiding catheter, and positioned as far as possible in the venous system, preferably in the (postero)lateral vein. After a minimum of 6 months of biventricular pacing, functional class of the patients was re-evaluated, and an extensive echocardiographic study was performed.

Statistical analysis

All continuous variables had normal distribution (as evaluated by Kolmogorov-Smirnov tests). Summary statistics for these variables are therefore presented as mean values ± one standard deviation (SD). Categorical data are summarized as frequencies and percentages. Differences in baseline characteristics between patients with and without LV dyssynchrony are evaluated using unpaired Student t-tests (continuous variables), Chi-square tests or Fisher's exact tests (dichotomous variables), as appropriate.

One-way Analysis of variance (ANOVA) with repeated measures was applied to evaluate differences in time-to-peak radial strain between the 6 segments at baseline and at follow-up within the separate cohorts of patients with and without LV dyssynchrony. Changes that occurred in the time-to-peak value between the baseline and follow-up visit were quantified, and differences in changes according to the presence or absence of LV dyssynchrony were then analyzed by one-way ANOVA as well. Subsequently, two-way ANOVA (with repeated measures for segments) was applied to study differences in time-to-peak radial strain patterns between patients with and without LV dyssynchrony. Univariable and multivariable logistic regression analyses were performed to identify possible predictors of LV dyssynchrony. The following variables were investigated: age, duration of atrial fibrillation, coronary artery disease, QRS duration at baseline, LV ejection fraction and follow-up duration. All variables entered the multivariable stage, irrespective of the results of the univariable analyses. Subsequently, the backward deletion method was applied to build the final regression model, and we intended to keep all variables with a p-value <0.15 in the model. We intended to report adjusted Odds Ratios (OR), however since no variable reached the pre-specified p<0.15 we report only the crude unadjusted OR with their corresponding 95% confidence intervals (CI).

Changes in LV function and LV size between the baseline and follow-up visit were quantified, and differences in these changes between patients with and without LV dyssynchrony were studied by unpaired Student t-tests. Changes in LV ejection fraction over the 3 different time points (baseline, RV pacing, biventricular pacing) for 11 patients who were upgraded to biventricular pacing, were analyzed with one-way ANOVA with Bonferroni post-hoc testing (3 repeated tests; p<0.0167 was considered significant for each test).

Analyses were performed using SPSS software (version 12.0, SPSS Inc. Chicago, Illinois, USA). All statistical tests were two-sided, and a p-value <0.05 was considered significant.

RESULTS

Study sample

Fifty-eight patients treated with His bundle ablation and pacemaker implantation were studied. The baseline characteristics of the study sample are listed in Table 1. In all patients the ablation and pacemaker implantation procedures were performed successfully. No complications related to the procedures were observed. Mean follow-up was 3.8 ± 2.0 years (range 1.2 to 8.7 years).

Table 1. Baseline characteristics of the study sample

	All patients (n=58)	LV dyssynchrony absent (n=25)	LV dyssynchrony present (n=33)	P value *
Age, years	61 ± 11	59 ± 11	63 ± 12	0.1
Gender, M/F	33 / 25	15 / 10	18 / 15	0.8
Duration of AF, years	7 ± 5	7 ± 5	6 ± 5	0.3
Previous used anti-arrhythmic drugs, n	3.2 ± 1.3	3.2 ± 1.5	3.2 ± 1.1	0.9
Hypertension, n (%)	26 (45%)	12 (48%)	14 (42%)	0.8
Severe MR (grade 3-4), n (%)	0 (0%)	0 (0%)	0 (0%)	1.0
Coronary artery disease, n (%)	8 (14%)	3 (12%)	5 (15%)	1.0
Previous myocardial infarction, n (%)	4 (7%)	1 (4%)	3 (9%)	0.6
NYHA functional class	1.7 ± 0.6	1.7 ± 0.6	1.8 ± 0.7	0.5
QRS duration, ms	99 ± 10	100 ± 11	99 ± 11	0.8

* As assessed with unpaired Student t-tests (continuous variables), Chi-square or Fisher's Exact tests (dichotomous variables), as appropriate. AF = atrial fibrillation; MR = mitral regurgitation; NYHA = New York Heart Association.

Strain analysis: Heterogeneity in time-to-peak radial strain

Time-to-peak radial strain was assessed for the 6 standard segments: septal, anteroseptal, anterior, lateral, posterior and inferior. A total of 762 segments were analyzed on the LV short-axis images. Of the 762 segments, 35 segments (5%) were excluded because of poor tracking scores. Subsequently, the site of earliest and latest mechanical activation throughout the cardiac cycle was determined. At baseline, there was a homogeneous distribution of the earliest and latest mechanical activated sites among the 6 segments (Figure 1, panel A). In contrast, after long-term permanent RV pacing, a marked heterogeneity in time-to-peak radial strain of the 6 segments was observed (Figure 1, panel B). The septal and the anteroseptal segments were most frequently the earliest activated segments (34% and 30% of the total earliest activated segments, respectively); whereas the lateral and posterior segments were only seldom the earliest activated sites (7% and 6%, respectively). In contrast, the lateral and posterior segments were most frequently the latest activated segments (31% and 25%, respectively); whereas the septal (5%) and the anteroseptal (6%) were rarely the latest activated segments (Figure 1).

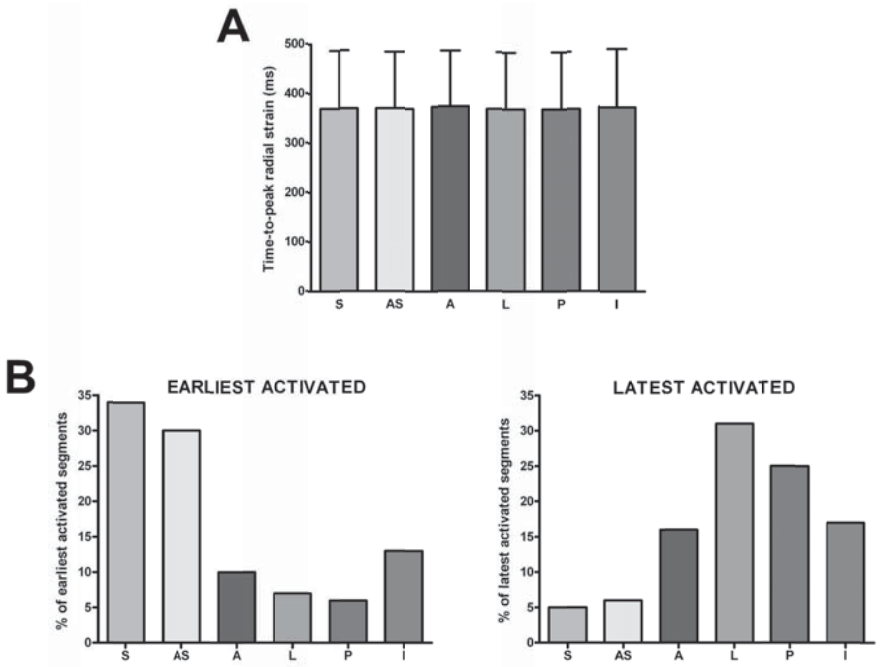

Figure 1. Distribution of time-to-peak radial strain among the 6 segments. Panel A: Time-to-peak radial strain was similar among the 6 standard segments at baseline. Panel B: Distribution of the sites of earliest and latest mechanical activation after permanent right ventricular pacing. The septal and anteroseptal segments were most frequently the sites of earliest mechanical activation, whereas the lateral and posterior segments were most frequently the sites of latest mechanical activation. A= anterior; AS = anteroseptal; I = inferior; L= lateral; P = posterior; S = septal.

LV dyssynchrony assessment with speckle tracking radial strain

The difference in time-to-peak radial strain between the 6 segments can be used to assess LV dyssynchrony. A time difference ≥130 ms between the time-to-peak radial strain of the (antero) septal and the posterolateral segments has been found to predict the response to cardiac resynchronization therapy (16). Therefore, we used this cut-off value to determine the presence of LV dyssynchrony. In Table 2, the time-to-peak radial strain values at baseline and at follow-up are shown with the study sample divided according to the presence or absence of LV dyssynchrony.

At baseline, strain curves revealed similar time-to-peak radial strain among the 6 segments (Table 2). Mean time-to-peak radial strain was 371 ± 114 ms for the 6 segments in all patients. There were no significant differences in time-to-peak radial strain among the 6 segments at baseline (Table 2). Accordingly, there was no significant delay between the (antero)septal and posterolateral segments (mean difference 26 ± 25 ms) Furthermore, the time difference between the earliest and the latest activated segments was 37 ± 31 ms. In none of the patients LV dyssynchrony, as represented by a time difference ≥130 ms between the (antero)septal and posterolateral segments, was present at baseline.

Table 2. Time-to-peak radial strain for the 6 segments at baseline and after permanent RV pacing

		Septal	Anteroseptal	Anterior	Lateral	Posterior	Inferior	P value among 6 segments *	P value between 2 groups †
Baseline	LV dyssynchrony absent (n=25), ms	375 ± 100	371 ± 101	373 ± 96	365 ± 98	365 ± 103	373 ± 104	0.06	0.5
	LV dyssynchrony present (n=33), ms	366 ± 131	369 ± 125	375 ± 125	370 ± 129	371 ± 126	373 ± 130	0.8	
Follow-up	LV dyssynchrony absent, ms	375 ± 72	389 ± 63	395 ± 64	389 ± 54	394 ± 57	379 ± 77	0.2	<0.001
	LV dyssynchrony present, ms	280 ± 120	287 ± 100	407 ± 76	453 ± 77	445 ± 93	374 ± 124	<0.001	
Δ Baseline to Follow-up	LV dyssynchrony absent, ms	+ 7 ± 126	+ 26 ± 128	+ 31 ± 119	+ 30 ± 113	+ 37 ± 116	+ 12 ± 145	0.09	<0.001
	LV dyssynchrony present, ms	- 80 ± 159	- 79 ± 164	+ 38 ± 154	+ 87 ± 157	+ 81 ± 144	+ 9 ± 148	<0.001	

* As assessed with one-way ANOVA. † As assessed with two-way ANOVA.

In contrast, after a mean of 3.8 ± 2.0 years of permanent RV pacing, radial strain curves revealed significant differences in time-to-peak radial strain among the 6 segments. In 33 (57%) patients there was a difference of ≥130 ms between the (antero)septal and posterolateral segments, indicating the presence of LV dyssynchrony. The study sample was subsequently divided in 2 groups: patients without LV dyssynchrony (n=25) and patients with LV dyssynchrony (n=33) after permanent RV pacing. There were no significant differences in baseline characteristics between the 2 groups (Table 1), and none of the variables that we considered were significantly associated with the development of LV dyssynchrony (Table 3). Duration of follow-up was similar between the patients with and without LV dyssynchrony (4.0 ± 2.0 years and 3.8 ± 2.0 years, respectively) and paced QRS duration at follow-up was not different between the patients with and without LV dyssynchrony (169 ± 20 ms vs. 167 ± 21 ms, p=0.8).

Table 3. Multivariable regression analysis for prediction of LV dyssynchrony

	OR (95% CI)	P value
Age *	0.97 (0.92 – 1.01)	0.1
Duration of AF *	1.06 (0.94 – 1.19)	0.3
Coronary artery disease	0.61 (0.14 – 2.74)	0.5
QRS duration	1.01 (0.96 – 1.06)	0.8
LV ejection fraction	0.98 (0.88 – 1.09)	0.7
Follow-up duration *	0.92 (0.71 – 1.20)	0.5

* ratio per year.

Radial strain after long-term permanent RV pacing

In the patients with LV dyssynchrony, time-to-peak radial strain was significantly shorter in the septal and anteroseptal segments, as compared to baseline values (septal 280 ± 120 ms vs. 366 ± 131 ms, p=0.014; anteroseptal 287 ± 100 ms vs. 369 ± 125 ms, p=0.019). In contrast, time-to-peak radial strain in the lateral and posterior segments was significantly longer, as compared to baseline values (lateral 453 ± 77 ms vs. 370 ± 129 ms, p=0.008; posterior 445 ± 93 ms vs. 371 ± 126 ms, p=0.007).

Conversely, in the patients without LV dyssynchrony, no significant differences in time-to-peak radial strain among the 6 segments were observed. Time-to-peak radial strain was longer for all 6 segments as compared to baseline, but no significant differences were detected (Table 2).

In addition to time-to-peak strain, peak radial strain was assessed for the 6 standard segments. At baseline, no differences were noted in peak radial strain among the 6 segments (septal 31 ± 14%, anteroseptal 32 ± 13%, anterior 32 ± 15%, lateral 33 ± 16%, posterior 33 ± 17% and inferior 33 ± 14%). In contrast, after long-term RV pacing, peak radial strain was significantly lower in the septal and the anteroseptal segments (21 ± 13%, p=0.007, and 24 ± 16%, p=0.039 respectively) and significantly higher in the lateral and posterior segments (43 ± 20%, p=0.030, and 42 ± 20%, p=0.040 respectively), whereas peak radial strain remained similar in the anterior (32 ± 20%) and inferior (32 ± 18%) segments, as compared to baseline. Interest-

ingly, no significant differences were noted between the patients with LV dyssynchrony and the patients without LV dyssynchrony.

Thirty-eight patients underwent echocardiography within 1 day after the pacemaker implantation as part of the clinical evaluation. Of these patients, 14 (37%) showed LV dyssynchrony immediately after pacemaker implantation. In addition, at follow-up tissue Doppler imaging was performed to confirm the presence or absence of LV dyssynchrony. All patients with LV dyssynchrony on speckle tracking analysis also had LV dyssynchrony on tissue Doppler imaging (mean 103 ± 21 ms). All patients without LV dyssynchrony on speckle tracking analysis also had no LV dyssynchrony on tissue Doppler imaging (mean 29 ± 22 ms).

At baseline and follow-up, NYHA functional class was assessed and echocardiographic evaluation was performed to assess LV volumes, diameters and LV systolic function. In the patients with LV dyssynchrony, NYHA functional class deteriorated from 1.8 ± 0.7 to 2.4 ± 0.7 ($p<0.001$), whereas NYHA class improved in the patients without LV dyssynchrony (from 1.7 ± 0.6 to 1.4 ± 0.6, $p=0.008$). The LV parameters as assessed with standard echocardiograms are listed in Table 4.

Table 4. Echocardiographic parameters of LV function and LV size at baseline and after RV pacing

	LV dyssynchrony absent (n=25)			LV dyssynchrony present (n=33)			
	Baseline	Follow-up	Δ	Baseline	Follow-up	Δ	P value *
LV ejection fraction, %	48 ± 5	51 ± 7	+ 4 ± 8	48 ± 5	39 ± 10	- 10 ± 11	<0.001
LV end-diastolic volume, ml	115 ± 27	119 ± 29	+ 3 ± 18	124 ± 38	158 ± 70	+ 34 ± 50	0.004
LV end-systolic volume, ml	60 ± 17	58 ± 18	- 3 ± 14	65 ± 24	99 ± 59	+ 37 ± 50	<0.001
LV end-diastolic diameter, cm	5.2 ± 0.7	5.4 ± 0.4	+ 0.1 ± 0.7	5.5 ± 0.9	6.0 ± 1.0	+ 0.4 ± 0.7	0.5
LV end-systolic diameter, cm	3.4 ± 0.6	3.5 ± 0.5	+ 0.1 ± 0.7	3.8 ± 0.9	4.4 ± 1.3	+ 0.5 ± 1.0	0.2
Fractional shortening, %	35 ± 9	35 ± 7	+ 1 ± 9	32 ± 11	27 ± 12	- 4 ± 13	0.8
Clinically relevant mitral regurgitation (grade 3-4), n (%)	0	2 (8%)	+ 2	0	5 (15%)	+ 5	0.7

* Difference between Δ values of patients with LV dyssynchrony vs. patients without LV dyssynchrony, as assessed with unpaired t tests for continuous variables and Fisher's Exact test for dichotomous variable.

Upgrading permanent RV pacing to biventricular pacing

In 11 patients, an upgrade of the conventional pacemaker to a biventricular pacing device was performed 4.1 ± 2.0 years after the His bundle ablation and pacemaker implantation procedure because of heart failure symptoms and the presence of LV dyssynchrony. The LV pacing lead was positioned in the mid lateral region in 3 patients (27%), and in the postero-lateral region in 8 patients (73%). After a mean of 11 ± 8 months, an extensive echocardiogram was performed to assess LV function and LV dyssynchrony.

In all patients, radial strain curves revealed disappearance of the LV dyssynchrony after upgrade to biventricular pacing. Time-to-peak radial strain for the different segments were: septal 373 ± 56 ms, anteroseptal 362 ± 53 ms, anterior 369 ± 53 ms, lateral 367 ± 54 ms, posterior 386 ± 43 ms, inferior 374 ± 48 ms. In none of the patients, a difference in time-to-peak radial strain ≥130 ms between the (antero)septal and posterolateral segments was present. A

representative example of the speckle tracking strain curves of a patient at the different time points is shown in Figure 2.

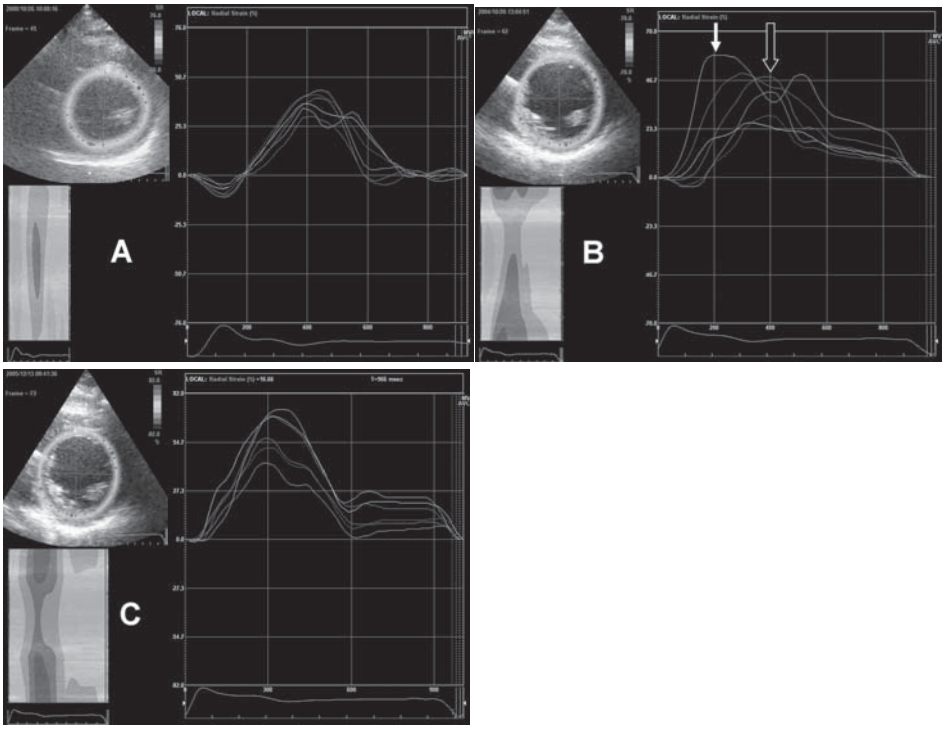

Figure 2. Radial strain curves assessed with speckle tracking analysis of a representative patient. The color-coded curves represent the 6 segments (light blue = septal; yellow = anteroseptal; red = anterior; green = lateral; purple = posterior; dark blue = inferior). Panel A: Before His bundle ablation and pacemaker implantation, there was no significant delay in time-to-peak radial strain among the 6 segments. Panel B: After 4 years of permanent RV pacing, a marked heterogeneity in time-to-peak strain for the 6 segments was observed. A time difference >130 ms was present between the time-to-peak radial strain of the septal (arrow) and posterolateral (open arrow) segments. Panel C: In this patient, upgrade of the conventional pacemaker to a biventricular pacemaker was performed. More than 1 year after 'upgrade', the radial strain curves revealed restoration of synchronous LV activation, with no significant delay between the time-to-peak radial strain of the different segments.

Of interest, mean LV ejection fraction improved from 30 ± 8% to 39 ± 7% ($p<0.001$) after upgrade to biventricular pacing. In all patients, an increase in LV ejection fraction ≥5% was observed. LV ejection fractions for the different time points in the 11 patients are demonstrated in Figure 3. In addition, the deleterious effects of RV apical pacing on LV volumes were partially reversed after upgrade to biventricular pacing. LV end-diastolic volume had decreased from 224 ± 66 ml to 167 ± 47 ml ($p=0.001$), and LV end-systolic volume had decreased from 160 ± 58 ml to 103 ± 34 ml ($p<0.001$) after upgrade to biventricular pacing. In all patients, a decrease in end-systolic volume ≥15% was observed. In addition, NYHA functional class improved after upgrade to biventricular pacing from 3.1 ± 0.3 to 2.1 ± 0.5 ($p<0.001$).

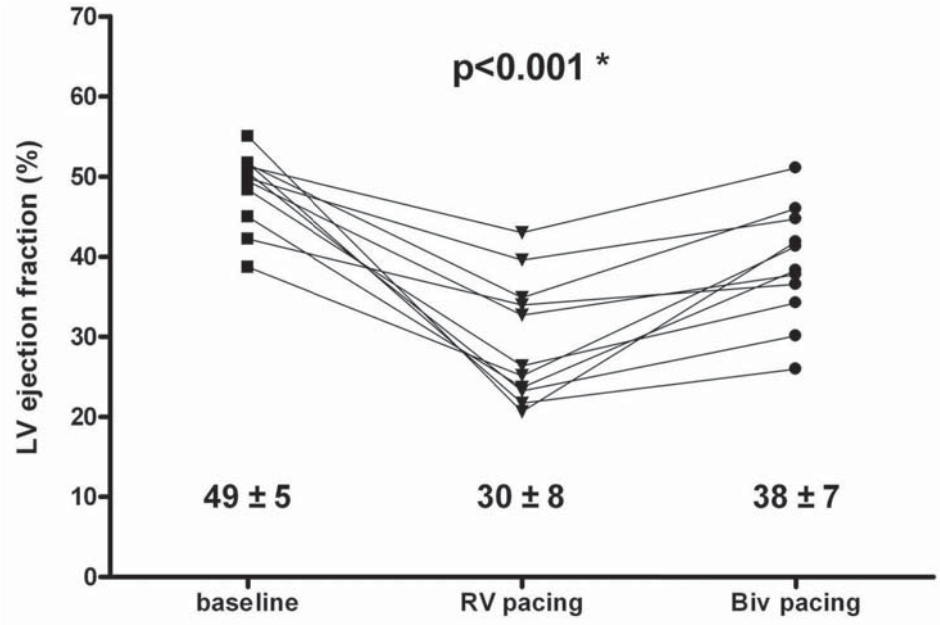

Figure 3. Effect of upgrading to biventricular pacing on left ventricular ejection fraction. LV ejection fraction at different time points for 11 patients who were upgraded to biventricular (BiV) pacing after a mean of 4.1 ± 2.0 years of permanent RV pacing. After permanent RV pacing, LV ejection fraction had significantly decreased. This was partly reversed after upgrade to biventricular pacing. * As assessed with repeated measures analysis of variance. Bonferroni post-hoc testing revealed significant differences between baseline and RV pacing ($p<0.001$) and between RV pacing and BiV pacing ($p<0.01$).

DISCUSSION

In the present study, speckle tracking revealed heterogeneity in time-to-peak radial strain and LV dyssynchrony in 57% of the patients with permanent RV pacing after His bundle ablation. The present study further extends our previous findings (11). Whereas previously myocardial velocities were assessed with tissue Doppler imaging (11), in the present study timing of regional LV strain was assessed with the use of speckle tracking. Frequently, strain analysis allows for more accurate analysis of LV function/dyssynchrony since it may permit differentiation between active contraction and passive motion. In addition, using this novel technique, accurate evaluation of LV dyssynchrony at baseline was possible, whereas in the previous study the M-mode derived septal-to-posterior wall motion delay was used (11). Most importantly, in the present study it was demonstrated that LV dyssynchrony induced by RV apical pacing could be reversed in patients receiving an 'upgrade' to biventricular pacing, with a concomitant improvement in LV function and functional class.

Strain analysis

In the present study, novel speckle tracking software applied to standard short-axis images was used to assess timing of regional wall strain, and identify regions of early and late activation in permanent RV paced patients. Speckle tracking radial strain is a novel technique that allows angle-independent measurement of regional strain and time-to-peak radial strain of different segments among the LV wall (12,13). This new technique has recently been validated using sonomicrometry and magnetic resonance imaging (18,19). Furthermore, it has been demonstrated that speckle tracking can quantify LV dyssynchrony, and accurately predict responders to cardiac resynchronization therapy (16). In addition, speckle tracking analysis allows for an accurate quantification of regional wall strain and time-to-peak wall strain, with a high reproducibility (20,21). In the current study, a good inter- and intra-observer agreement for this novel technique was noted.

Using speckle tracking radial strain, induction of heterogeneity in strain after RV pacing was demonstrated, with a short time-to-peak radial strain of the anteroseptal segments and a long time-to-peak radial strain of the posterolateral segments. At present, no studies have been reported concerning the effects of permanent RV apical pacing on timing of regional wall strain in patients. In contrast, several animal studies have reported wall strain analysis during RV pacing (8-10). Wyman et al (8) used magnetic resonance imaging tagging to evaluate regional wall strain in 7 dogs during RV apical pacing. Similar to the present findings, the authors demonstrated an early activation of the septum with late activation of the lateral wall during RV apical pacing. Dohi et al (10) studied the effect of RV and biventricular pacing in 8 dogs using angle-corrected tissue Doppler strain imaging. The authors reported similar heterogeneity in activation with short time-to-peak strain in the septal segments (189 ± 55 ms) and long time-to-peak strain in the free wall (487 ± 37 ms) during RV pacing.

Furthermore, in the present study regional wall strain analysis revealed that the site of earliest mechanical activation was mainly located at the (antero)septum, whereas the site of latest activation was mainly located at the posterolateral wall. In a mapping study in 40 patients, Vassallo et al (22) demonstrated that the site of earliest activation in the left ventricle during RV pacing was consistently located in the septum. In addition, the authors demonstrated that the site of latest activation during RV apical pacing varied (22), but was predominantly located in the posterior wall. The current observations are in line with this study: 64% of the earliest activated segments were located in the (antero)septum, and 56% of the latest activated segments were located in the posterolateral wall (Figure 1).

A significant time difference between the earliest and latest time-to-peak radial strain represents intraventricular conduction delay or LV dyssynchrony. Previously, a time difference ≥130 ms between the (early) septal and the (late) posterior wall, as assessed with speckle tracking radial strain, has been demonstrated to be a good predictor for response to cardiac resynchronization therapy (16). Interestingly, in the present study not all patients exhibited a significant delay between the earliest activated (antero)septum and the latest activated posterolateral

wall. In 53% of the patients, significant LV dyssynchrony was present after long-term RV pacing. Furthermore, time-to-peak radial strain in the patients without LV dyssynchrony was later in all segments as compared to the non-paced baseline value. Thus, the exact effect of RV apical pacing may differ per patient. This may be related to the fact that the electrical impulses propagate more slowly through the myocardium during RV pacing than through the Purkinje system during normal sinus rhythm. However, it remains unclear why some patients develop significant LV dyssynchrony, and others do not. There were no differences in baseline characteristics between the two groups, and mean follow-up duration was similar in the two groups. Importantly, a multivariable logistic regression analysis including age, duration of atrial fibrillation, coronary artery disease, QRS duration at baseline, LV ejection fraction and follow-up duration was not able to identify any predictor for the development of LV dyssynchrony in the present study. Future studies are needed to identify the patients who are more vulnerable for the detrimental effects of permanent RV apical pacing. Furthermore, more studies are needed to determine whether LV dyssynchrony is induced acutely with RV apical pacing or develops over time.

Impact of RV pacing on LV function and heart failure symptoms

Recently, several trials have stressed the deleterious effects of RV apical pacing. In the DAVID trial (3), DDDR pacing increased the risk of death or heart failure hospitalization, as compared to VVIR back-up pacing in 506 patients with an indication for implantable cardioverter defibrillator therapy. Similarly, the MOST trial (4) demonstrated that the cumulative percent ventricular pacing was a strong predictor of heart failure hospitalization in patients with DDDR and VVIR pacing. The aforementioned studies suggest that RV apical pacing should be avoided. However, the exact mechanism of the detrimental effect of RV apical pacing remains unclear in these studies. The present study shows that the decrease in LV systolic function and NYHA functional class is directly related to the presence of LV dyssynchrony. Previously, it has been suggested that the detrimental effects of RV apical pacing may be more pronounced in patients with LV dysfunction before pacemaker implantation (4). However, in the present study no differences in baseline characteristics between the patients with and the patients without LV dyssynchrony were found.

Effects of upgrade to biventricular pacing

To reverse the abnormal activation pattern (i.e. LV dyssynchrony) induced by RV pacing, biventricular pacing could be considered. In the present study, 11 patients received 'upgrade' of the conventional pacemaker to biventricular pacing. LV dyssynchrony, induced by RV apical pacing, largely resolved with a concomitant improvement in LV function and NYHA functional class. Leon et al (23) reported similar results in 20 patients with severe heart failure and prior atrioventricular node ablation and permanent RV pacing. Following upgrade to biventricular pacing, LV ejection fraction improved from 22 ± 7% to 31 ± 12%, and NYHA class improved from 3.4 ± 0.5 to 2.4 ± 0.6. The HOBIPACE trial (24) recently demonstrated that in 30 patients

with standard pacemaker indication and LV dysfunction, biventricular pacing was superior to conventional RV pacing regarding LV systolic function (ejection fraction biventricular 34.8 ± 8.9% vs. RV pacing 28.5 ± 11.2%, p<0.001), NYHA functional class (biventricular 1.9 ± 0.6 vs. RV pacing 2.5 ± 0.7, p<0.05) and exercise capacity (peak oxygen consumption biventricular 14.0 ± 3.0 ml/min/kg vs. RV pacing 12.5 ± 2.9 ml/min/kg, p<0.001).

In addition, alternate pacing sites (such as RV outflow tract, paraHisian or direct His bundle pacing) have been proposed to replace RV apical pacing (2). Several short-term studies have reported a modest benefit of RV outflow tract, as compared to RV apical pacing (25). Furthermore, paraHisian (26) and direct His bundle pacing (27) have been proven to be feasible. However, concerns about long-term lead stability at the various sites exist, and no large randomized trials on long-term benefit over RV apical pacing have been reported. Still, alternate pacing sites may prevent the occurrence of LV dyssynchrony as induced by RV apical pacing, and therefore could be considered in patients who need permanent pacing.

Limitations

In the present study only 6 segments at the mid-ventricular level were analyzed using radial strain analysis. Analysis at more basal and apical levels and analysis of circumferential or longitudinal strain may provide additional information on the effects of RV apical pacing on LV function. Nonetheless, it has been demonstrated that radial strain analysis at the mid-ventricular level is of great value for the detection of LV dyssynchrony and the prediction of response to cardiac resynchronization therapy (16). Additional head-to-head comparisons are needed to determine which type of strain analysis (radial, longitudinal or circumferential) provides optimal information.

CONCLUSIONS

Speckle tracking radial strain revealed that permanent RV pacing induced heterogeneity in time-to-peak strain among the LV walls (with early activation in the (antero)septal and late activation in the posterolateral segments). In 57% of patients, this resulted in the presence of LV dyssynchrony. In these patients a deterioration of LV systolic function and NYHA functional class was observed. Upgrade to biventricular pacing resulted in (partial) reversal of these detrimental effects of RV pacing.

REFERENCES

1. Healey JS, Toff WD, Lamas GA et al. Cardiovascular outcomes with atrial-based pacing compared with ventricular pacing: meta-analysis of randomized trials, using individual patient data. Circulation 2006;114:11-7.
2. Manolis AS. The deleterious consequences of right ventricular apical pacing: time to seek alternate site pacing. Pacing Clin Electrophysiol 2006;29:298-315.
3. Wilkoff BL, Cook JR, Epstein AE et al. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. JAMA 2002;288:3115-23.
4. Sweeney MO, Hellkamp AS, Ellenbogen KA et al. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. Circulation 2003;107:2932-7.
5. Steinberg JS, Fischer A, Wang P et al. The clinical implications of cumulative right ventricular pacing in the multicenter automatic defibrillator trial II. J Cardiovasc Electrophysiol 2005;16:359-65.
6. Vernooy K, Dijkman B, Cheriex EC, Prinzen FW, Crijns HJ. Ventricular remodeling during long-term right ventricular pacing following His bundle ablation. Am J Cardiol 2006;97:1223-7.
7. Tse HF, Yu C, Wong KK et al. Functional abnormalities in patients with permanent right ventricular pacing: the effect of sites of electrical stimulation. J Am Coll Cardiol 2002;40:1451-8.
8. Wyman BT, Hunter WC, Prinzen FW, McVeigh ER. Mapping propagation of mechanical activation in the paced heart with MRI tagging. Am J Physiol 1999;276:H881-H891.
9. Prinzen FW, Hunter WC, Wyman BT, McVeigh ER. Mapping of regional myocardial strain and work during ventricular pacing: experimental study using magnetic resonance imaging tagging. J Am Coll Cardiol 1999;33:1735-42.
10. Dohi K, Pinsky MR, Kanzaki H, Severyn D, Gorcsan J, III. Effects of radial left ventricular dyssynchrony on cardiac performance using quantitative tissue Doppler radial strain imaging. J Am Soc Echocardiogr 2006;19:475-82.
11. Tops LF, Schalij MJ, Holman ER, van Erven L, van der Wall EE, Bax JJ. Right ventricular pacing can induce ventricular dyssynchrony in patients with atrial fibrillation after atrioventricular node ablation. J Am Coll Cardiol 2006;48:1642-8.
12. Reisner SA, Lysyansky P, Agmon Y, Mutlak D, Lessick J, Friedman Z. Global longitudinal strain: a novel index of left ventricular systolic function. J Am Soc Echocardiogr 2004;17:630-3.
13. Leitman M, Lysyansky P, Sidenko S et al. Two-dimensional strain-a novel software for real-time quantitative echocardiographic assessment of myocardial function. J Am Soc Echocardiogr 2004;17:1021-9.
14. Schiller NB, Shah PM, Crawford M et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. J Am Soc Echocardiogr 1989;2:358-67.
15. Thomas JD. How leaky is that mitral valve? Simplified Doppler methods to measure regurgitant orifice area. Circulation 1997;95:548-50.
16. Suffoletto MS, Dohi K, Cannesson M, Saba S, Gorcsan J, III. Novel speckle-tracking radial strain from routine black-and-white echocardiographic images to quantify dyssynchrony and predict response to cardiac resynchronization therapy. Circulation 2006;113:960-8.
17. Bax JJ, Bleeker GB, Marwick TH et al. Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy. J Am Coll Cardiol 2004;44:1834-40.
18. Langeland S, Wouters PF, Claus P et al. Experimental assessment of a new research tool for the estimation of two-dimensional myocardial strain. Ultrasound Med Biol 2006;32:1509-13.
19. Notomi Y, Lysyansky P, Setser RM et al. Measurement of ventricular torsion by two-dimensional ultrasound speckle tracking imaging. J Am Coll Cardiol 2005;45:2034-41.
20. Amundsen BH, Helle-Valle T, Edvardsen T et al. Noninvasive myocardial strain measurement by speckle tracking echocardiography: validation against sonomicrometry and tagged magnetic resonance imaging. J Am Coll Cardiol 2006;47:789-93.

21. Cho GY, Chan J, Leano R, Strudwick M, Marwick TH. Comparison of two-dimensional speckle and tissue velocity based strain and validation with harmonic phase magnetic resonance imaging. Am J Cardiol 2006;97:1661-6.
22. Vassallo JA, Cassidy DM, Miller JM, Buxton AE, Marchlinski FE, Josephson ME. Left ventricular endocardial activation during right ventricular pacing: effect of underlying heart disease. J Am Coll Cardiol 1986;7:1228-33.
23. Leon AR, Greenberg JM, Kanuru N et al. Cardiac resynchronization in patients with congestive heart failure and chronic atrial fibrillation: effect of upgrading to biventricular pacing after chronic right ventricular pacing. J Am Coll Cardiol 2002;39:1258-63.
24. Kindermann M, Hennen B, Jung J, Geisel J, Bohm M, Frohlig G. Biventricular versus conventional right ventricular stimulation for patients with standard pacing indication and left ventricular dysfunction: the Homburg Biventricular Pacing Evaluation (HOBIPACE). J Am Coll Cardiol 2006;47:1927-37.
25. de Cock CC, Giudici MC, Twisk JW. Comparison of the haemodynamic effects of right ventricular outflow-tract pacing with right ventricular apex pacing: a quantitative review. Europace 2003;5:275-8.
26. Occhetta E, Bortnik M, Magnani A et al. Prevention of ventricular desynchronization by permanent para-Hisian pacing after atrioventricular node ablation in chronic atrial fibrillation: a crossover, blinded, randomized study versus apical right ventricular pacing. J Am Coll Cardiol 2006;47:1938-45.
27. Deshmukh P, Casavant DA, Romanyshyn M, Anderson K. Permanent, direct His-bundle pacing: a novel approach to cardiac pacing in patients with normal His-Purkinje activation. Circulation 2000;101:869-77.