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ORIGINAL RESEARCH

The Detrimental Effect of RA Pacing on LA Function and Clinical Outcome in Cardiac Resynchronization Therapy

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ABSTRACT

OBJECTIVES This study assessed the impact of right-atrial (RA) pacing on left-atrial (LA) physiology and clinical outcome.

BACKGROUND Data for the effects of RA pacing on LA synchronicity, function, and structure after cardiac resynchronization therapy (CRT) are scarce.

METHODS The effect of RA pacing on LA function, morphology, and synchronicity was assessed in a prospective imaging cohort of heart failure (HF) patients in sinus rhythm with a guideline-based indication for CRT. Additionally, in a retrospective outcome cohort of consecutive HF patients undergoing CRT implantation, the relationship to RA pacing was assessed using various outcome endpoints. High versus low atrial pacing burden was defined as atrial pacing above or below 50% in both cohorts.

RESULTS A total of 36 patients were included in the imaging cohort (68 ± 11 years of age). Six months after CRT, patients with high RA pacing burden showed less improvement in LA maximum and minimum volumes and total emptying fraction ($p < 0.05$). Peak atrial longitudinal strain and reservoir and booster strain rates but not conduit strain rate improved after CRT in patients with low RA pacing burden but worsened in patients with high RA pacing burden ($p < 0.05$ for all). A high RA pacing burden induced significant intra-atrial dyssynchrony (maximum opposing wall delay: 44 ± 13 ms vs. 97 ± 17 ms, respectively; $p = 0.022$). A total of 569 patients were included in the outcome cohort. After covariate adjustments were made, a high RA pacing burden was associated with reduced LV reverse remodeling ($\beta = 8.738$; 95% confidence interval [CI]: 3.101 to 14.374; $p = 0.002$) and new-onset or recurrent atrial fibrillation (41% vs. 22%, respectively, at a median of 31 months [range 22 to 44 months follow-up]; $p < 0.001$). There were no differences in time to first HF hospitalization or all-cause mortality ($p = 0.185$) after covariate adjustment. However, in a recurrent event analysis, HF readmissions were more common in patients exposed to a high RA pacing burden ($p = 0.003$).

CONCLUSIONS RA pacing in CRT patients negatively influences LA morphology, function, and synchronicity, which is associated with worse clinical outcome, including diminished LV reverse remodeling, increased risk for new-onset or recurrent AF and heart failure readmission. Strategies reducing RA pacing burden may be warranted. (J Am Coll Cardiol Img 2019;■:■-■) © 2019 by the American College of Cardiology Foundation.

Interest is increasing in left atrium (LA) function as a modulator of disease in heart failure (HF). The LA functions as a highly dynamic continuum of the left ventricle (LV), modulating LV filling and securing optimal cardiac performance, functioning as a reservoir, a conduit, and a booster pump (**Figure 1A**) (1). In order to adequately exert its function, the LA depends on the timely and organized

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ABBREVIATIONS AND ACRONYMS

CRT = cardiac resynchronization therapy

HFrEF = heart failure with reduced ejection fraction

LA = left atrium

LVEF = left ventricular ejection fraction

LVESV = left ventricular end systolic volume

MR = mitral regurgitation

NYHA = New York Heart Association

PALS = peak atrial longitudinal strain

RA = right atrium

contraction and relaxation off all different LA walls (1).

Cardiac resynchronization therapy (CRT) improves symptoms, functional status, and clinical outcome in selected HF patients. The salutary effects of CRT are partially mediated by the induction of LV reverse remodeling (2,3). More recently it has been recognized that CRT not only induces significant LV reverse remodeling but also induces LA reverse remodeling, with the latter being related to clinical outcome and development of atrial arrhythmia episodes (4–6); yet this LA reverse remodeling often occurs to a variable degree and does not occur in all patients (6).

For right ventricular pacing, it is well established that a higher burden of ventricular pacing (e.g., >40%) induces interventricular and intraventricular dyssynchrony, compromising LV function (7,8). However, few data are available if right atrial (RA) pacing induces a similar degree of dyssynchrony at the level of the LA, which potentially compromises LA function. This study sought to determine the effects of RA pacing on LA function and its relationship with various clinical outcome parameters.

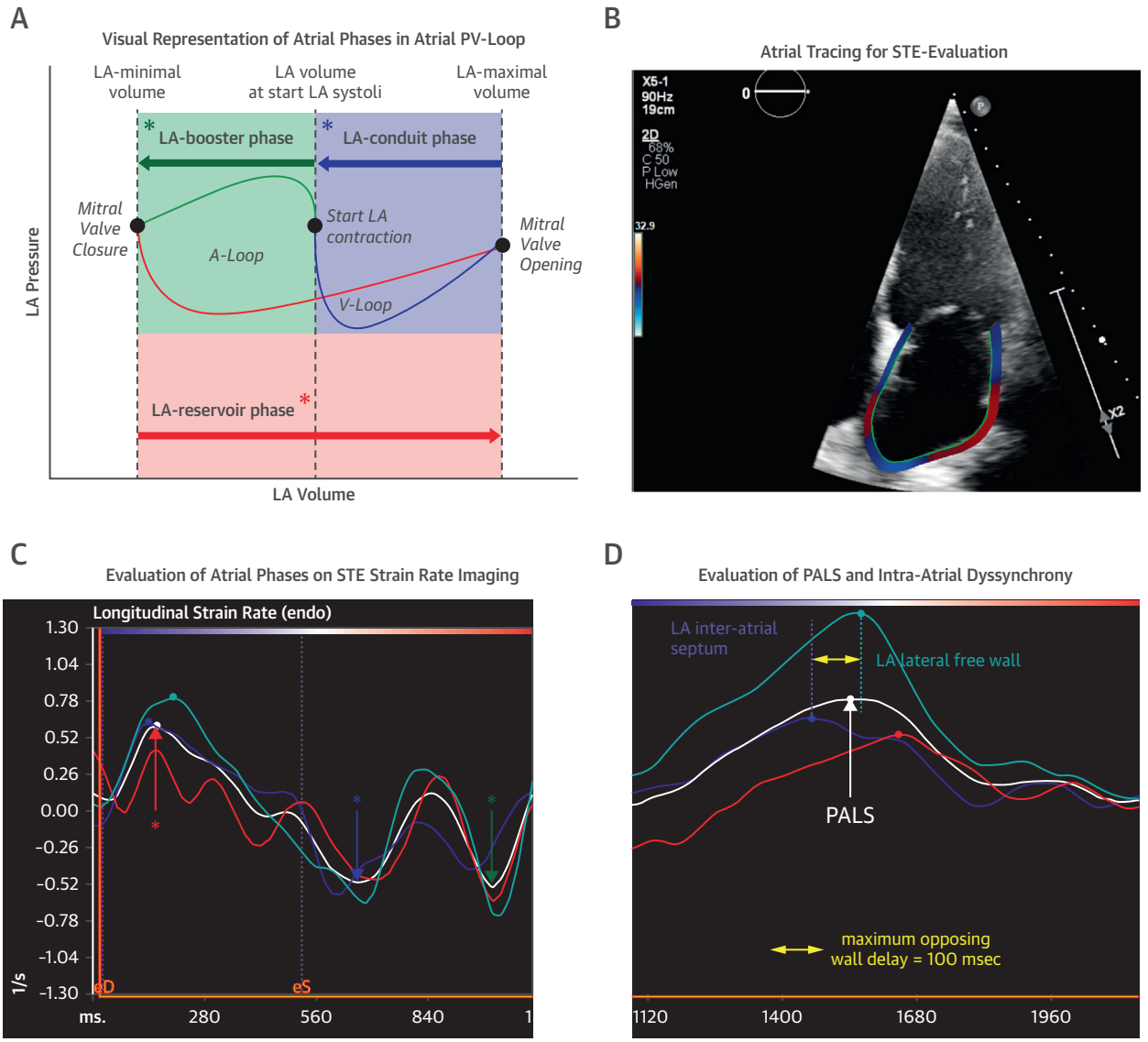
METHODS

STUDY POPULATION. To assess the relationship between RA pacing and the effects on LA function and outcome, 2 different cohorts were studied. First, a prospective imaging cohort was studied to mechanistically assess the hemodynamic effects of RA pacing on LA reverse remodeling in CRT recipients. Second, a retrospective CRT outcome cohort was studied to assess the relationship between the degree of atrial pacing and clinical outcome. Inclusion criteria for the prospective imaging cohort included the following: 1) symptomatic HF (New York Heart Association [NYHA] functional class ≥II); 2) LV ejection fraction (LVEF) below 35% despite optimal medical therapy; 3) electrical dyssynchrony defined as QRS duration >130 ms; and 4) all patients had to be in sinus rhythm at implantation and during follow-up echocardiography. Patients in the imaging cohort were included between October 2016 and February 2018. The retrospective outcome cohort consisted of all consecutive HF with reduced EF (HFrEF) patients undergoing CRT implantation in the tertiary HF clinic, Ziekenhuis Oost Limburg, between October 2008 and September 2016. Indications for CRT were followed in accordance with European Society of Cardiology guidelines (9). In order to reliably assess the impact of RA pacing on LA function, the authors specifically chose to study CRT patients, as isolated right ventricular pacing can also affect LA function (10). Therefore, patients with a classic pacemaker or implantable cardioverter-defibrillator were not included.

DEVICE IMPLANTATION, OPTIMIZATION, AND INTERROGATION. Devices were implanted according to standard practice, with the LV lead placed transvenously in a posterolateral coronary sinus branch. The RA lead was always placed in the right atrial appendage, and the right ventricular lead was positioned at the right ventricular apex. The day after implantation, all patients in both the imaging and the outcome cohorts underwent device optimization according to a standard protocol as previously published (11). Briefly, the iterative method was used for optimizing the atrioventricular interval and the LV offset was adapted to ensure a difference between left and right ventricular pre-ejection time of <30 ms. Because all patients were in sinus rhythm at implantation, devices were programmed in a DDD mode, with the lower rate ranging between 50 and 60 beats/min (10). At every device interrogation, the amount of atrial pacing was registered and averaged over the entire study period, which was 6 months for the imaging cohort and the entire follow-up period for the outcome cohort. The diagnosis of new-onset or recurrent atrial fibrillation (AF) was based on device-registered electrograms and was defined as previously published (4).

IMAGE ACQUISITION AND STORAGE. Comprehensive 2-dimensional (2D) echocardiography examinations were performed using a commercially available system (model IE33/EPIQ 7, Philips Medical Systems, Andover, Massachusetts). Standard 2D and Doppler echocardiographic images were acquired by experienced cardiac sonographers (P.M., M.D., and W.M.). In both cohorts, images were acquired at baseline and at 6 months follow-up. Echocardiographic images from the imaging cohort were stored as Digital Imaging and Communications in Medicine (DICOM) files on a secured server and analyzed off-line using third-party software (Image arena version 4.6, TomTec Imaging Systems GmbH, Unterschleissheim, Germany). Echocardiographic results in the outcome cohort were obtained from the echocardiographic reports validated by certified sonographers from periodic follow-up examinations. All echocardiographic parameters were measured according to American Society of Echocardiography guidelines (12).

FIGURE 1 **Methods of LA Function Assessment and Its relation to LA Physiology**



(A, C) The LA acts as a reservoir for pulmonary venous return (reservoir phase: **red arrow with asterisks**). This function is influenced by the contraction of the LV corresponding to a downward movement of the mitral annulus toward the LV apex, besides intrinsic atrial relaxation and stiffness, all of which might be modulated by LA synchronicity. In early LV diastole and diastasis, blood flows passively from the LA to the LV (conduit phase: **blue arrow with asterisks**), which is related to LV relaxation. Finally, the LA actively contracts, which augments ventricular filling (booster phase: **green arrow with asterisks**). The latter reflects the magnitude and timing of intrinsic LA contractility. **(B)** Automated tracking of the LA endocardial. **(D)** PALS (**white line with white arrow**) and maximum opposing wall delay (**yellow arrow**). LA = left atrium/atrial; LV = left ventricular; PALS = peak atrial longitudinal strain; PV = pressure-volume; STE = speckle-tracking echocardiography.

ANALYSIS OF LA MORPHOLOGY, FUNCTION, AND SYNCHRONICITY IN THE IMAGING COHORT. LA maximum and minimum volumes were measured using the modified Simpson rule. LA total emptying fraction was calculated as [(LA maximal volume – LA minimal volume)/ LA maximal volume]. Furthermore, LA phasic functions were assessed using strain and strain rate imaging derived from 2D speckle-tracking echocardiography (2D-STE). This technique allows quantification of all 3 components of the atrial phase (Figure 1). High-quality apical 4-chamber views over 3 consecutive cardiac cycles were recorded and stored for subsequent off-line analysis. Sector width was kept at a minimum to

optimize frame rate, and LA foreshortening was avoided. Echocardiographic analysis of phasic LA functions was performed off-line by an echo reader (S.D.) who was blinded to other study-related parameters including the degree of atrial pacing and clinical outcome. Offline speckle tracking analysis of LA phasic functions was performed using a commercially available third-party vendor-independent software (2D cardiac performance analysis, Image Arena version 4.6, TomTec Imaging Systems). End-diastole and end-systole were manually defined as the frame before closure and opening of the mitral valve. The ventricular cycle was used as a reference (i.e., R-R gated speckle tracking was performed with the QRS complex at a zero reference point). After manually tracing the endocardial LA border in the 4-chamber view in end-diastole, automated tracking of the endocardial borders throughout the subsequent frames of the selected beat followed. Adequate tracking of the region of interest on the contour was verified. Peak atrial longitudinal strain (PALS) was determined as the peak positive strain value during late systole on the averaged longitudinal strain curve (**Figure 1D**). The (positive) reservoir strain rate in late systole, (negative) conduit strain rate in early diastole, and (negative) pump strain rate were determined from the averaged LA longitudinal strain rate curves (**Figure 1**). Intra-atrial LA mechanical dyssynchrony was assessed as the time to peak longitudinal strain in the opposing portions of the LA wall (interatrial septum versus free lateral wall), measured in standard 4-chamber echocardiographic views (maximum opposing wall delay) (**Figure 1D**) (13).

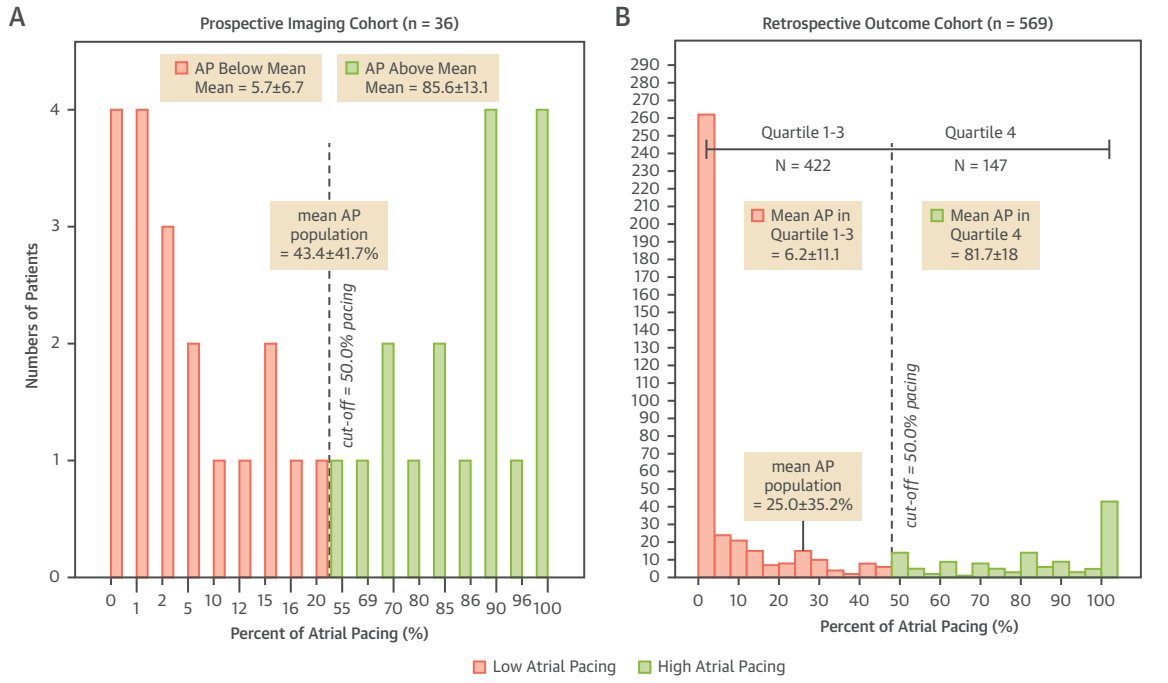
CLINICAL ENDPOINTS IN THE OUTCOME COHORT. In the outcome cohort, the relationship between atrial pacing and adverse clinical outcome after CRT implantation was assessed. Outcome parameters of interest included the following: 1) echocardiographic reverse remodeling at 6 months after CRT; 2) symptomatic improvement 6 months after CRT; 3) occurrence of new-onset AF (as defined above); and 4) occurrence of the combined endpoint of HF hospitalization and all-cause mortality in a time-to-first-event analysis and HF readmissions in a separate recurrent event analysis. As echocardiographic parameters assessing reverse remodeling following CRT, the reduction in LV end-systolic volume (LVESV) and the reduction in degree of mitral regurgitation (MR) were used, both on a continuous scale. MR quantitation was performed using an integrated approach in the outcome cohort, using methods left to the discretion of the sonographers, with classification afterward on a scale of 0 to 4, indicating no, slight, mild, moderate, and severe MR.

STATISTICS. Continuous variables are expressed as mean ± SD if normally distributed or median (interquartile range) if non-normally distributed. Categorical data were expressed as numbers and proportions and compared using the Fisher exact test. Continuous variables were compared using the Student *t*-test or Mann-Whitney *U* test as appropriate. To account for numerical difference in baseline LA echocardiography values in the imaging cohort, an ANCOVA model was built to assess the change in LA echocardiography parameters, adjusting for baseline values (low versus high RA pacing = fixed effect; whereas baseline echocardiography values = random effect). The distribution of atrial pacing in the imaging and outcome cohorts were visually inspected. A cutoff threshold above and below 50% of atrial pacing was chosen (high versus low atrial pacing burden), as this results is a split above and below the mean in the imaging cohort. A binary logistic regression model was built to determine the incidence of AF (both recurrent and new onset). A sensitivity analysis was performed that excluded patients with a paroxysmal AF history to establish whether RA pacing was a true predictor of new-onset AF in addition to AF recurrence. Variables with a p value below 0.10 in the univariate model were included in the stepwise forward multivariate model. Linear regression and binary logistic regression analysis were used to determine whether a higher burden of RA pacing was an independent predictor of less LV reverse remodeling. Kaplan-Meier curves were constructed using the log-rank test used to test differences in event rate for the combined endpoint time to first HF admission or all-cause mortality. Cox proportional multivariate adjustment was performed to determine the independent effect of atrial pacing on the combined endpoint of HF hospitalization and all-cause mortality after adjusting for differences in baseline characteristics. Additionally, HF readmissions were assessed as recurrent events, using a marginal means model adjusted for differences in baseline characteristics as described previously (14). The recurrent events between a low and a high burden of atrial pacing rate ratio was assessed using post hoc least significant difference testing. Statistical significance was always set at a 2-tailed probability level of <0.05. Statistical analyses were performed using SPSS version 22 software (IBM, Armonk, New York).

RESULTS

ATRIAL PACING IN THE IMAGING AND OUTCOME COHORT. A total of 36 patients were prospectively included in the imaging cohort. A flowchart showing

FIGURE 2 **Distribution of Percent of Atrial Pacing in Imaging and Outcome Cohort**



(A) Distribution of RA pacing burden in the imaging cohort and outcome cohort. **Boxes** indicate mean atrial pacing in the entire population and in the population with low RA pacing **(pink)** and high RA pacing burden **(green)**. AP = atrial pacing; other abbreviations as in Figure 1.

the patient selection method is reflected in Supplemental Figure 1. The distribution of atrial pacing in the imaging cohort is shown in **Figure 2A**. Patients with <50% of atrial pacing (low pacing burden) were exposed to a mean of 5.7% of atrial pacing, whereas patients with atrial pacing above the 50% threshold were exposed to a mean of 85.6% of atrial pacing (high pacing burden). Baseline characteristics are shown in **Table 1**. The percent of biventricular pacing at 6 months was similar in the low and high atrial pacing burden groups (98 ± 1.2 vs. 99 ± 1.0, respectively; p = 0.334). In the outcome cohort, a total of 831 patients received implants between October 2008 and September 2016. Of those, 262 patients (32%) were excluded from the analysis because 89 patients underwent a His-bundle ablation, and 95 patients were in permanent AF at the time of implantation, and therefore the impact of atrial pacing could not be examined. A total of 78 patients had missing pivotal data. Therefore, the final study population consisted of 569 patients. Median follow-up duration was 31 months (interquartile range 22 to 44 months). The mean atrial pacing exposure over this time frame is shown in **Figure 2B**. A total of 422 patients had an atrial pacing burden below 50% and 147 had an atrial pacing burden above 50%, exposed to 6.2% and 81.7% of atrial pacing, respectively. Both groups achieved a similar degree of biventricular pacing (99 ± 1.0 and 99 ± 1.1, respectively; p = 0.594) during follow-up. Baseline characteristics of the outcome cohort are shown in **Table 2**.

ATRIAL PACING NEGATIVELY INFLUENCES ATRIAL MORPHOLOGY, FUNCTION, AND SYNCHRONICITY. Detailed echocardiographic analysis of LA morphology, function, and synchronicity at baseline and 6 months were acquired in all patients in the imaging cohort. Supplemental Table 1 demonstrates intra- and interobserver variabilities, illustrating good agreement of these measurements (all ICC >0.897). The impact of atrial pacing was assessed by handling atrial pacing as a binary value (above or below 50% of atrial pacing) (**Central Illustration**) and as a continuous parameter (Supplemental Figure 2). Baseline values of LA morphologic and functional parameters are shown in **Table 1**. Six months after CRT implantation, LA reverse remodeling was apparent only in patients with a low burden of atrial pacing. In contrast, patients with a high burden of atrial pacing exhibited progressive enlargement of LA volumes and a deterioration in PALS, reservoir and

TABLE 1 Baseline Characteristics of Imaging Cohort

	Total Population (N = 36)	High Atrial Pacing Burden (n = 17)	Low Atrial Pacing Burden (n = 19)	p Value
Demographics				
Age, yrs	68 ± 11	71 ± 10	65 ± 13	0.106
Male	28 (78%)	11 (65%)	17 (90%)	0.074
Etiology of heart failure				0.516
Ischemic	19 (53%)	8 (47%)	11 (58%)	
Nonischemic	17 (47%)	9 (53%)	8 (42%)	
NYHA functional class				0.396
II	17 (49%)	7 (41%)	10 (56%)	
III	18 (51%)	10 (59%)	8 (44%)	
Hypertension	17 (47%)	9 (53%)	8 (42%)	0.516
Diabetes	13 (36%)	9 (53%)	4 (21%)	0.047
Dyslipidemia	21 (58%)	12 (71%)	9 (47%)	0.158
Clinical characteristics				
Heart rate, beats/min	62 ± 10	62 ± 10	62 ± 11	0.207
Weight, kg	80 ± 17	80 ± 15	81 ± 14	0.810
BMI, kg/m^2	28 ± 5	29 ± 5	27 ± 4	0.288
SBP, mmHg	126 ± 19	132 ± 19	126 ± 24	0.466
DBP, mmHg	72 ± 10	75 ± 8	71 ± 9	0.139
eGFR, ml/min/1.73 m^2	60 ± 24	62 ± 23	65 ± 26	0.686
NT-proBNP, pg/ml	1,068 (509-2,122)	807 (519-2,102)	1,303 (477-2,219)	0.654
ECG/device features				
QRS-duration, ms	158 ± 28	159 ± 32	156 ± 27	0.759
LBBB morphology	30 (83%)	14 (82%)	16 (84%)	0.881
Non-LBBB morphology	6 (17%)	3 (18%)	3 (16%)	0.881
CRT-defibrillator	21 (58%)	7 (41%)	14 (74%)	0.070
CRT-pacemaker	15 (42%)	10 (59%)	5 (26%)	0.070
Heart failure medication				
ACEI or ARB	33 (92%)	15 (88%)	18 (95%)	0.481
Beta-blocker	31 (86%)	12 (71%)	19 (100%)	0.011
MRA	28 (78%)	11 (65%)	17 (90%)	0.074
Loop diuretic	14 (39%)	5 (30%)	9 (47%)	0.270
Baseline LA echo				
LA minimal volume, ml	51 ± 33	42 ± 23	63 ± 37	0.064
LA maximum volume, ml	84 ± 38	77 ± 33	94 ± 41	0.203
LA emptying fraction, %	43 ± 16	47 ± 15	37 ± 14	0.054
LA PALS, %	17 ± 9	19 ± 10	13 ± 5	0.033
LA reservoir SR, s^{-1}	0.59 ± 0.25	0.61 ± 0.27	0.49 ± 0.17	0.137
LA conduit SR, s^{-1}	−0.59 ± 0.29	−0.61 ± 0.30	−0.61 ± 0.30	0.963
LA booster SR, s^{-1}	−0.59 ± 0.51	−0.74 ± 0.61	−0.45 ± 0.41	0.198

Values are mean ± SD or n (%).

ACE = angiotensin angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; CRT = cardiac resynchronization therapy; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; LBBB = left bundle branch block; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; SBP = systolic blood pressure.

booster phase strain rates (Central Illustration A and B). The conduit strain rate (reflecting LV suction) was not affected by atrial pacing. To account for the numerical difference in baseline values, the p value was adjusted for the baseline-value in an ANCOVA model (Central Illustration A and B) (p values were adjusted). In addition, RA appendage pacing perturbs intra-atrial LA synchronicity between the interatrial septum and LA free wall (indicated by the increase in maximum opposing wall delay) (Central Illustration C).

ATRIAL PACING AND THE VENTRICULAR RESPONSE TO CRT. Six months after CRT implantation, patients in the outcome cohort with a low burden of atrial pacing had more improvement in NYHA functional class (p = 0.007) (Supplemental Figure 3). Table 3 illustrates the changes in echocardiographic parameters assessing LV systolic and diastolic function and filling, from baseline to 6 months follow-up in the imaging cohort. A higher burden of RA pacing was associated with less LV remodeling (i.e., improvement in parameters of systolic LV function) potentially suggesting that LA intra-atrial dys-synchrony and diminished LA function limits the LV recruitable preload. Figure 3A and 3B illustrate the association between atrial pacing and a reduction in LVESV and MR in the outcome cohort, indicating an association between LV volumetric remodeling and atrial pacing. After adjustment in a linear regression model for differences in baseline characteristics, a higher burden of RA pacing remained associated with less LV remodeling (β = 8.738; 95% confidence interval [CI]: 3.101 to 14.374; p = 0.002) and less reduction in MR (β = 0.503; 95% CI: 0.358 to 0.648; p < 0.001). Furthermore, Supplemental Tables 2 and 3 illustrate the results of a linear regression model for change in LVESV and MR after correction for both known predictors of reverse remodeling after CRT and differences in baseline characteristics. Although Supplemental Tables 4 and 5 illustrate binary logistic regression models for the endpoint of LV reverse remodeling following CRT (defined as a reduction of LVESV above 15%), after accounting for similar predictors, modeling both atrial pacing in a categorical and continuous fashion.

ATRIAL PACING AND NEW-ONSET ATRIAL FIBRILLATION. Figure 3C shows that, during a median follow-up of 31 months (interquartile range 22 to 44 months), patients with a higher RA pacing burden had a higher incidence of AF (41% vs. 22%, respectively; p < 0.001). Table 4 illustrates a robust multivariate binary logistic regression model assessing predictors of AF incidence (new-onset or recurrent AF if patients had a history of a paroxysmal AF), showing that patients with a high atrial pacing burden had higher odds for developing new-onset or recurrent AF. Supplemental Tables 6 and 7 illustrates the results of a sensitivity analysis excluding the 133 patients (of the total 569) with a history of paroxysmal AF, indicating that, in patients without a history of paroxysmal AF, a higher burden of RA pacing predicted new-onset AF.

ATRIAL PACING AND HEART FAILURE HOSPITALIZATION AND ALL-CAUSE MORTALITY. Figure 3D illustrates the Kaplan-Meier curve for the combined endpoint of HF hospitalization and all-cause mortality in the outcome cohort, showing that higher atrial pacing is associated with a higher event rate ($p < 0.002$). Median follow-up of the entire population was 31 months (22 to 44 months). However, as reflected in Table 5, after adjustment for baseline characteristics, this difference in time to first HF event or all-cause mortality was nonsignificant ($p = 0.185$). Nevertheless, as indicated by Kaplan-Meier curves and the number of patients at risk, the event rate was relatively low (92 events; 16%; consisting of 84 HF readmissions and 8 deaths). In addition to time-to-event analysis, assessment of recurrent HF events was performed as patients are potentially chronically exposed to RA pacing. Supplemental Table 8 shows the marginal means model for the recurrent event analysis. Post hoc testing indicated a statistically higher rate ratio of recurrent events in patients with a high (rate ratio: 0.380; 95% CI: 0.273 to 0.486) versus low burden of atrial pacing (rate ratio: 0.189; 95% CI: 0.126 to 0.251; $p = 0.003$).

TABLE 2 Baseline Characteristics of Outcome Cohort

	Total Population (N = 569)	High Atrial Pacing Burden (n = 147)	Low Atrial Pacing Burden (n = 422)	p Value
Demographics				
Age, yrs	71 ± 10	73 ± 9	70 ± 11	0.013
Male	374 (66%)	100 (68%)	274 (65%)	0.495
Etiology of heart failure				0.210
Ischemic	334 (59%)	80 (54%)	254 (60%)	
Nonischemic	234 (41%)	67 (46%)	167 (40%)	
NYHA functional class				0.286
II	224 (40%)	59 (40%)	164 (39%)	
III	331 (58%)	84 (57%)	248 (59%)	
IV	14 (2%)	5 (3%)	6 (2%)	
Hypertension	470 (83%)	127 (86%)	343 (81%)	0.159
Diabetes	149 (26%)	33 (22%)	116 (27%)	0.430
Dyslipidemia	406 (71%)	106 (72%)	300 (71%)	0.814
Clinical characteristics				
Heart rate, beats/min	68 ± 17	67 ± 19	69 ± 16	0.281
Weight, kg	77 ± 16	76 ± 15	77 ± 15	0.730
BMI, Kg/m^2	27 ± 5	27 ± 5	27 ± 5	0.536
SBP, mmHg	123 ± 16	123 ± 15	123 ± 16	0.937
DBP, mmHg	71 ± 11	71 ± 10	71 ± 11	0.415
eGFR, ml/min/1.73 m^2	64 ± 24	56 ± 24	66 ± 23	<0.001
ECG/device features				
QRS-duration, ms	154 ± 27	152 ± 30	154 ± 25	0.480
LBBB morphology	434 (77%)	99 (67%)	335 (80%)	0.002
Non-LBBB morphology	131 (23%)	48 (33%)	83 (20%)	0.002
History of atrial fibrillation	133 (23%)	47 (32%)	86 (20%)	0.004
CRT-defibrillator	298 (52%)	68 (46%)	203 (48%)	0.624
CRT-pacemaker	256 (45%)	79 (54%)	219 (52%)	0.624
Heart failure medication				
ACEI or ARB	489 (86%)	124 (84%)	365 (87%)	0.521
Beta-blocker	473 (83%)	118 (80%)	355 (84%)	0.283
MRA	369 (65%)	93 (63%)	276 (65%)	0.640
Loop diuretic	239 (42%)	69 (47%)	170 (40%)	0.102

Values are mean ± SD or n (%).
Abbreviations are as in Table 1.

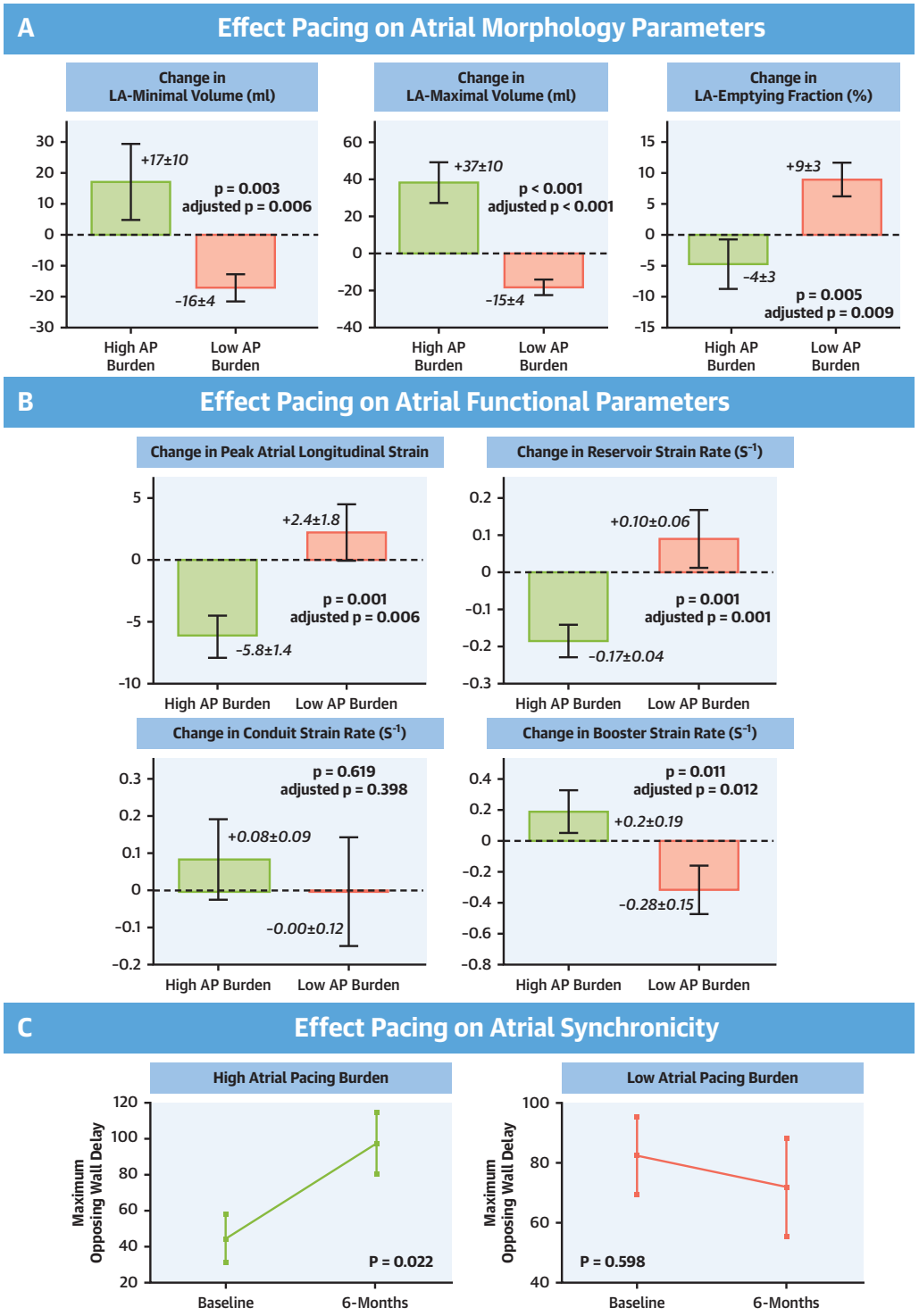
DISCUSSION

The present study adds important novel information about the effect of RA pacing on LA function and the association with outcome in HFrEF patients undergoing CRT. The main findings are the following: 1) a higher RA pacing burden is associated with a negative effect on LA reverse remodeling following CRT, as it associates with worsening of LA morphology, LA functional parameters (mainly affecting the LA reservoir phase and booster phase), and LA synchronicity; 2) a higher RA pacing burden is associated with less LV reverse remodeling; and 3) atrial pacing in CRT patients is associated with a higher risk for new-onset or recurrent AF and HF readmission but not all-cause mortality after covariate adjustment.

With advances in novel imaging techniques, interest is increasing in the function and structure of the LA in various cardiac disease entities. In HFrEF patients undergoing CRT specifically, it is acknowledged that CRT not only induces LV but also LA reverse remodeling (4-6,15,16). Although the beneficial changes at the level of the LA are often more pronounced in patients exhibiting significant LV reverse remodeling, it is important to understand that LA function is not only a reflection of LV systolic and diastolic functions. Indeed, intrinsic LA properties could also contribute to a variable LA reverse remodeling response in CRT recipients (1). This has been highlighted by a recent subanalysis of the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) trial showing that >20% of CRT patients had a discordant reverse remodeling response between the LA and LV (6). In that aspect, this study tried to mechanistically investigate the relationship between LA function after CRT in relation to the burden of RA pacing as a potentially modifiable factor.

Analysis of the imaging cohort indicates that CRT recipients who are exposed to a higher burden of RA pacing exhibit a worsening LA synchronicity which is associated with progressive LA enlargement and worsening of function and structure. Although extrapolation of the well-established detrimental effect of right ventricular pacing on LV function to the level of the atria seems logical, almost no such data

CENTRAL ILLUSTRATION **Effect of Atrial Pacing on LA Morphology, LA Function, and LA Synchronicity in the Imaging Cohort**



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(A) Change in LA morphology parameters. **(B)** Change in LA functional parameters. **(A, B)** Values indicate the change between baseline and 6 months follow-up. Adjusted p value is from the ANCOVA model. **(C)** Change from baseline to 6 months follow-up. p Value derived from the paired *t*-test. **green** = AP pacing >50%; **pink** = AP pacing <50%. **Bars** indicate mean change. **Error bars** indicate standard errors of the mean.

TABLE 3 Echocardiographic CRT Response Parameters in Relationship to Atrial Pacing

	High AP Burden (n = 17)			Low AP Burden (n = 19)			
	Baseline	Follow-up	Delta	Baseline	Follow-up	Delta	p Value
LVEF	31.7 ± 4	43.6 ± 9	11.9 ± 10*	28.2 ± 5	44.7 ± 11	16.5 ± 9*	0.018
LVEDV	163 ± 67	151 ± 56	−12 ± 75	246 ± 95	173 ± 71	−71 ± 75*	0.033
LVESV	112 ± 48	90 ± 50	−23 ± 64	177 ± 71	101 ± 57	−76 ± 59*	0.017
Aortic VTI	26.2 ± 15	27.3 ± 16	1.1 ± 22	20 ± 11	25 ± 7	5.2 ± 14	<0.001
E	78.7 ± 30	74.6 ± 32	−4.1 ± 29	81.3 ± 30	66.6 ± 23	−14.6 ± 17*	0.030
A	81.0 ± 19	64.9 ± 14	−16.1 ± 11*	71.3 ± 31	84.7 ± 28	13.3 ± 11*	<0.001
E/A	0.93 ± 0.47	1.20 ± 0.75	0.27 ± 0.3*	1.38 ± 0.92	0.86 ± 0.56	−0.52 ± 0.4*	0.041
Dt	232 ± 70	251 ± 77	19 ± 103	200 ± 53	241 ± 84	41 ± 77*	0.518
DFT%	39.3 ± 13	39.7 ± 5	0.3 ± 14	37.5 ± 14	55.6 ± 8	18 ± 17*	0.005

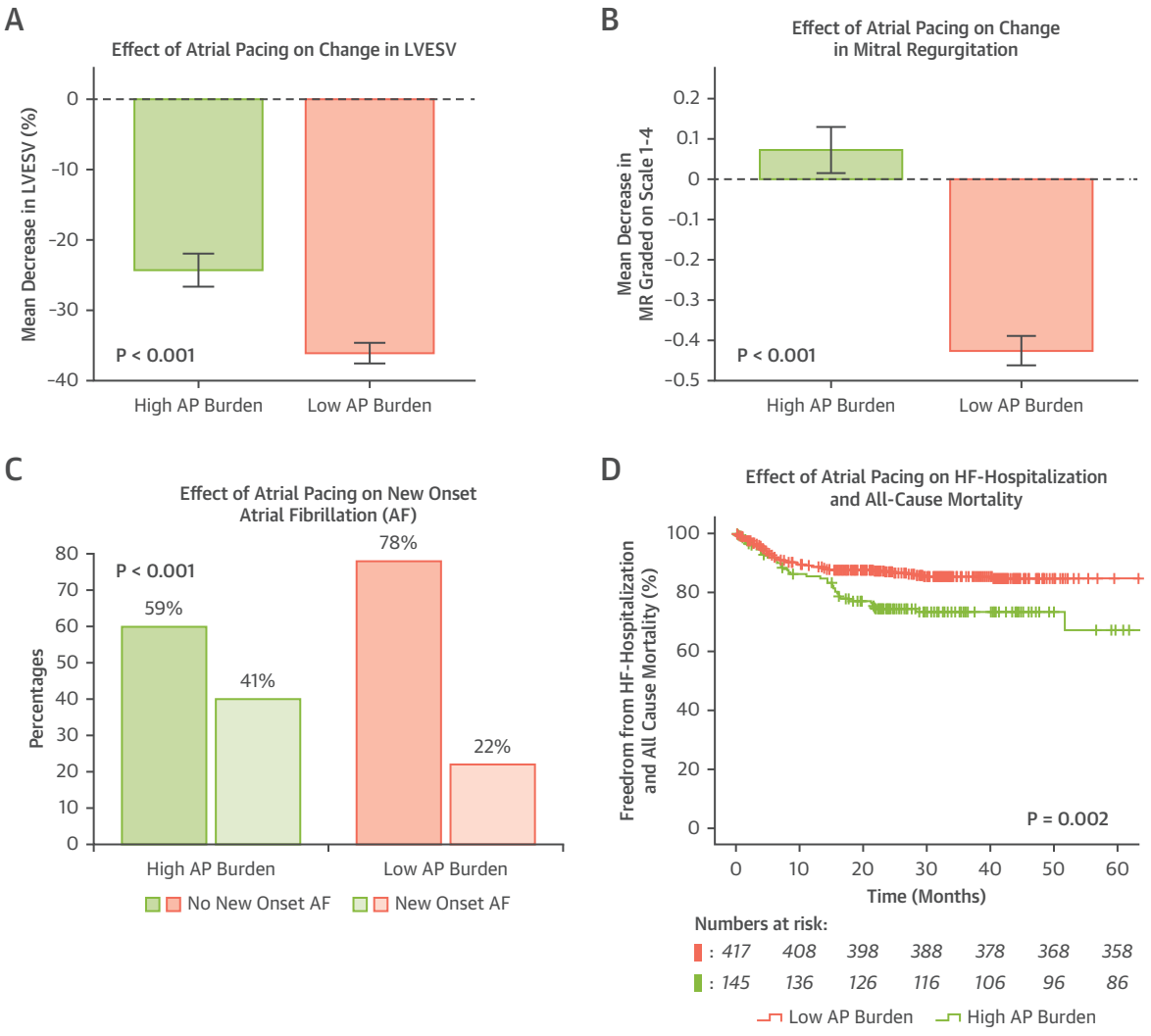
Values are mean ± SD. *Values indicate a significant longitudinal change from baseline to follow-up using paired *t* tests. The p values are from Student *t*-tests (delta values were normally distributed) or Mann-Whitney *U* test (delta values were not normally distributed) between the delta values from patients with low burden of atrial pacing versus those with a high burden of atrial pacing.

DFT% = diastolic filling time adjusted for the RR-interval (DFT values are expressed as a percents of the cardiac cycle); Dt = deceleration time; LVEDV = left ventricular end diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end systolic volume; VTI = velocity time integral.

are available (8). To the best of the present authors' knowledge, only Liang et al. (17) have assessed the acute hemodynamic effects of atrial pacing versus atrial sensing in CRT patients, illustrating that an atrial paced mode is associated with the generation of intra-atrial dyssynchrony and limits the LA preload contribution of the LV stroke volume. However, no data were available if chronic RA pacing was detrimental for LA structure and function. Additionally, this study used tissue Doppler imaging analysis which is prone to numerous technical issues. Furthermore, when switching from a sensed to a paced mode, an increase in lower rate is necessary to assure pacing above intrinsic heart rate, complicating the hemodynamic analysis as heart rate is not similar (17). The present analysis shows that a higher RA pacing burden is associated with atrial dyssynchrony, which may result in a diminished LA reverse remodeling response and worsening of atrial function and structure. Atrial pacing seems to be both detrimental to the LA reservoir phase and the LA booster phase but not the conduit phase. This is perhaps not surprising as the conduit phase is an expression of LV suction/filling, which is not expected to be influenced by intra-atrial dyssynchrony. When examining the mitral inflow pattern, a low pacing burden was indeed associated with an improvement in the contribution of the A-wave to ventricular filling, and the diastolic filling time improved significantly more in comparison to that in patients with a high burden of atrial pacing. Such an improved LA-diastolic and -systolic function may indeed result in a more optimal contribution to the LV preload (higher volumes at lower pressures), potentially explaining the more pronounced improvement in aortic velocity time integral. Although the latter is difficult to disentangle from an effect of more pronounced LV reverse remodeling witnessed in the low atrial pacing burden group.

In addition, the present analysis of the outcome cohort suggests that the burden of atrial pacing is importantly associated with diverse clinical outcome endpoints. Although LA reverse remodeling has been described as a predictor of LV reverse remodeling in CRT (and vice versa), no data are available for how the burden of atrial pacing affects response to CRT. This study now illustrates that a high burden of atrial pacing independently associates with less symptomatic improvement and less LV reverse remodeling (reduction in LVESV and reduction in MR). Furthermore, the increase in atrial volumes may contribute to ongoing secondary MR due to annular dilation. Next to CRT response, atrial pacing was also associated with new-onset AF and AF recurrence. Indeed, both in patients with a history of paroxysmal AF before CRT implantation and in patients without a history of AF, a higher RA pacing burden predicted AF-recurrence, respectively, new-onset AF. These findings are in line with those from a study by Adelstein et al. (18) and Sade et al. (19). Although atrial reverse remodeling has been shown to be an independent predictor of adverse hard outcome (HF hospitalization and mortality) in CRT patients, in a time-to-first-event analysis adjusted for baseline differences, a high RA pacing burden was associated only with a trend toward a higher event rate (5). Additionally, as the RA pacing burden represents a chronic exposure, a time-to-first event may capture less harm signal. Therefore, this study also assessed recurrent HF events, illustrating that a high RA pacing burden is associated with more HF readmission even after covariate adjustment.

FIGURE 3 **Effect of Atrial Pacing on Clinical Outcome in the Outcome Cohort**



(A) Change in LVESV. **(B)** Change in MR. **(C)** Occurrence of AF. **(D)** Kaplan-Meier curve for the combined endpoint of HF admission and all-cause mortality. **Bars** indicate mean change. **Error bars** indicate standard errors of the mean. AF = atrial fibrillation; HF = heart failure; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation.

Although our findings are novel and interesting from a pathophysiologic viewpoint, an equally important aspect for clinical practice is the fact that atrial pacing can sometimes be a modifiable factor. Several interventions could limit the degree of atrial pacing/dyssynchrony: First, adjustment of the lower rate below the intrinsic rate (when feasible) might promote atrial sensing instead of atrial pacing. Second, CRTs theoretically could be programed in an atrial sensing mode (VDD) instead of the frequently used DDD mode. Although VDD pacing may lead to retrograde atrial activation, which should be prevented, 1 study suggests that VDD versus DDD pacing in CRT is acutely associated with an improved LV filling and myocardial performance and is associated with less atrial dyssynchrony (20). Finally, alternative pacing sites instead of the right atrial appendage may be preferred locations for right atrial lead placement. Indeed, pacing at the level of conduction fibers interconnecting the RA and LA (Bachman bundle) or at the coronary sinus ostium might limit inter- and intra-atrial dyssynchrony. Clearly in studies that target RA, pacing burden is necessary to truly determine if RA pacing is a true predictor of LA function and outcome. Indeed, it could also be hypothesized that a higher burden is a manifestation of an

TABLE 4 Multivariate Adjustment of Atrial Pacing Burden on New-Onset and Recurrent AF

	Univariate Binary Logistic Regression			Multivariate Binary Logistic Regression		
	OR	95% CI	p Value	OR	95% CI	p Value
Atrial pacing*	0.292	0.092–0.926	**0.037**	**3.412**	**1.279–9.174**	**0.014**
Age, yrs†	1.012	0.953–1.074	0.705			
eGFR, ml/min†	1.012	0.989–1.037	0.313			
LBBB‡	10.718	0.897–116.49	**0.051**	8.778	1.000–79.760	0.051
Previous AF‡	4.624	1.557–13.733	**0.006**	**4.157**	**1.592–10.855**	**0.004**
BMI, kg/m^2†	1.121	0.984–1.278	**0.087**	1.121	0.984–1.278	0.087
Male	1.425	0.468–4.340	0.534			
NYHA functional class§	1.751	0.687–4.461	0.240			
Previous stroke‡	0.720	0.119–4.346	0.720			
Hypertension‡	1.716	0.437–6.745	0.439			
Type 2 diabetes‡	0.287	0.072–1.144	**0.077**	0.287	0.072–1.144	0.077
Dyslipidemia‡	0.796	0.206–3.070	0.740			
Baseline LVEF†	1.034	0.962–1.111	0.365			
Baseline LA diameter†	0.818	0.397–1.683	0.585			

*Atrial pacing was modeled as a binary value comparing high burden (>50%) with a low burden (<50%). †Continuous covariate with units as defined in the table. ‡Binary covariate structure. §Categorical values comparing low with high NYHA functional classes.

AF = atrial fibrillation; CI = confidence interval; LBBB = left bundle branch block; LA = left atrial; LVEF = left ventricular ejection fraction; OR = odds ratio; other abbreviations as in Table 1.

underlying different atrium, less amenable for reverse remodeling and associated with clinical outcome. Indeed, some baseline characteristics were present in this study, which the present authors tried to overcome by using various statistical adjustment techniques. However, only studies targeting RA pacing in a randomized and blinded fashion are able to determine a true causal relationship.

STUDY LIMITATIONS. First, due to its retrospective design, the atrial parameters could not be determined in the outcome cohort. Second, assessment of LA function by STE-derived strain and strain rate depend heavily on image quality and frame rate. Nevertheless, this study does indicate excellent interobserver and intraobserver agreement. Third, the distribution of atrial pacing was more skewed in the outcome cohort than in the imaging cohort, which may indicate some sampling bias in the imaging cohort. However, handling atrial pacing as a continuous parameter always generated concordant findings. Fourth, development of AF is a time -dependent variable and could best be approached in a Cox proportional regression hazard model. However precise timing of AF development was not always available as AF was registered during device periodic follow-ups and not necessarily the precise date. Fifth, data for chronotropic incompetence were not available and therefore are not able to give finite answers why patients received more atrial pacing. Finally, some baseline differences were present in the imaging cohort and the outcome cohort regarding baseline characteristics. However, the authors tried to optimally correct for this by using corrections techniques (ANCOVA models and multivariate models).

TABLE 5 Adjusted Effect of a High Atrial Pacing Burden on Clinical Outcome in Time to Event Analysis

	Adjusted HR	95% CI	p Value
Atrial pacing*	1.346	0.867–2.090	0.185
Difference in baseline characteristics:			
Age, yrs*	1.022	0.996–1.048	0.094
Atrial fibrillation†	1.585	1.019–2.465	0.041
eGFR, ml/min*	0.981	0.971–0.991	<0.001
LBBB†	0.628	0.398–0.990	0.045

*Atrial pacing was modeled as a binary value comparing high burden (>50%) with a low burden (<50%). †Continuous covariate with unit defined in the table.

HR = hazard ratio; other abbreviations as in Table 1.

CONCLUSIONS

The degree of RA pacing in CRT patients negatively influences left atrial synchronicity, which is associated with worsening of functional and morphologic LA parameters. Moreover, atrial pacing is independently associated with less functional and structural CRT response and associated with a higher risk for new-onset and recurrent AF and HF readmissions but not all-cause mortality.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Our analysis illustrates that right atrial pacing results in LA intra-atrial dyssynchrony which is associated with a deterioration in left atrial morphology parameters and a deterioration in atrial function. In a large outcome cohort, this was associated with a higher risk of developing AF, diminished reverse remodeling following CRT and more HF readmissions. Studies are necessary to determine if avoidance of unnecessary right atrial pacing results in improved clinical outcome.

TRANSLATIONAL OUTLOOK: Additional studies are necessary to confirm the result, further investigating if a reduction of right atrial pacing beneficially influences LA function and morphology. Strategies that could reduce RA pacing include avoiding the programming of an unnecessary high baseline pacing rate above the intrinsic heart rate. Studies investigating if pacing in the RA in anatomic distinct locations (e.g., near Bachman bundle) improves inter and intra-atrial synchronicity in comparison to standard right atrial appendage pacing, are warranted.

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KEY WORDS atrial fibrillation, cardiac resynchronization therapy, left atrial function, reverse remodeling, right atrial pacing

APPENDIX For an expanded Methods as well as supplemental figures and tables, please see the online version of this paper.