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ORIGINAL RESEARCH ARTICLE

Arrhythmic Risk in Biventricular Pacing Compared With Left Bundle Branch Area Pacing: Results From the I-CLAS Study

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BACKGROUND: Left bundle branch area pacing (LBBAP) may be associated with greater improvement in left ventricular ejection fraction and reduction in death or heart failure hospitalization compared with biventricular pacing (BVP) in patients requiring cardiac resynchronization therapy. We sought to compare the occurrence of sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) and new-onset atrial fibrillation (AF) in patients undergoing BVP and LBBAP.

METHODS: The I-CLAS study (International Collaborative LBBAP Study) included patients with left ventricular ejection fraction ≤35% who underwent BVP or LBBAP for cardiac resynchronization therapy between January 2018 and June 2022 at 15 centers. We performed propensity score–matched analysis of LBBAP and BVP in a 1:1 ratio. We assessed the incidence of VT/VF and new-onset AF among patients with no history of AF. Time to sustained VT/VF and time to new-onset AF was analyzed using the Cox proportional hazards survival model.

RESULTS: Among 1778 patients undergoing cardiac resynchronization therapy (BVP, 981; LBBAP, 797), there were 1414 propensity score–matched patients (propensity score–matched BVP, 707; propensity score–matched LBBAP, 707). The occurrence of VT/VF was significantly lower with LBBAP compared with BVP (4.2% versus 9.3%; hazard ratio, 0.46 [95% CI, 0.29–0.74]; $P<0.001$). The incidence of VT storm (>3 episodes in 24 hours) was also significantly lower with LBBAP compared with BVP (0.8% versus 2.5%; $P=0.013$). Among 299 patients with cardiac resynchronization therapy pacemakers (BVP, 111; LBBAP, 188), VT/VF occurred in 8 patients in the BVP group versus none in the LBBAP group (7.2% versus 0%; $P<0.001$). In 1194 patients with no history of VT/VF or antiarrhythmic therapy (BVP, 591; LBBAP, 603), the occurrence of VT/VF was significantly lower with LBBAP than with BVP (3.2% versus 7.3%; hazard ratio, 0.46 [95% CI, 0.26–0.81]; $P=0.007$). Among patients with no history of AF (n=890), the occurrence of new-onset AF >30 s was significantly lower with LBBAP than with BVP (2.8% versus 6.6%; hazard ratio, 0.34 [95% CI, 0.16–0.73]; $P=0.008$). The incidence of AF lasting >24 hours was also significantly lower with LBBAP than with BVP (0.7% versus 2.9%; $P=0.015$).

CONCLUSIONS: LBBAP was associated with a lower incidence of sustained VT/VF and new-onset AF compared with BVP. This difference remained significant after adjustment for differences in baseline characteristics between patients with BVP and LBBAP. Physiological resynchronization by LBBAP may be associated with lower risk of arrhythmias compared with BVP.

Key Words: arrhythmias, cardiac ■ atrial fibrillation ■ cardiac pacing, artificial ■ cardiac resynchronization therapy ■ defibrillators, implantable ■ tachycardia, ventricular

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Clinical Perspective

What Is New?

- Left bundle branch area pacing was associated with significantly lower incidence of sustained ventricular tachycardia or ventricular fibrillation compared with biventricular pacing in patients undergoing cardiac resynchronization therapy.
- Left bundle branch area pacing was also associated with significantly lower incidence of new-onset atrial fibrillation compared with biventricular pacing in patients undergoing cardiac resynchronization therapy.

What Are the Clinical Implications?

- Physiological resynchronization using left bundle branch area pacing may lower the incidence of atrial and ventricular arrhythmias compared with biventricular pacing.
- The reduced arrhythmogenicity associated with conduction system pacing needs to be confirmed in randomized clinical trials.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
BVP	biventricular pacing
CRT	cardiac resynchronization therapy
HF	heart failure
HR	hazard ratio
ICD	implantable cardioverter defibrillator
LBBAP	left bundle branch area pacing
LBBB	left bundle branch block
LV	left ventricular
LVEF	left ventricular ejection fraction
PS	propensity score
VF	ventricular fibrillation
VT	ventricular tachycardia
VTA	ventricular tachy-arrhythmia

Cardiac resynchronization therapy (CRT) using biventricular pacing (BVP) is an effective therapy for patients with reduced left ventricular ejection fraction (LVEF), heart failure (HF) symptoms, widened QRS, or frequent ventricular pacing. CRT has been shown to reduce HF hospitalizations and all-cause mortality.[1] Observational studies more recently have shown that conduction system pacing and specifically left bundle branch area pacing (LBBAP) may have improved responder rates compared with traditional BVP.[2–4]

More effective resynchronization and establishment of physiological ventricular activation may have additional beneficial effects on ventricular as well as atrial tachyarrhythmias in patients undergoing CRT. Furthermore, ventricular proarrhythmia associated with epicardial coronary venous pacing used in conventional CRT can potentially be avoided during physiological His bundle or LBBAP.[5]

The recently published observational study I-CLAS (International Collaborative LBBAP Study) demonstrated that LBBAP was associated with improved clinical outcomes among patients undergoing CRT implantation with regard to HF hospitalizations and all-cause mortality.[6] The objective of this substudy is to compare the occurrence of ventricular arrhythmias and new-onset atrial fibrillation (AF) among patients undergoing CRT implantation by BVP and LBBAP in a propensity score–matched cohort.

METHODS

The design and primary results of the study were previously published.[6] This was a multicenter, international, observational, retrospective case-control study designed to evaluate the real-world clinical outcomes in BVP versus LBBAP. Included were patients who underwent successful CRT implantation with a class I or II CRT indication (New York Heart Association Class II–IV symptoms, ejection fraction <35%, QRS>130 ms, or frequent ventricular pacing). All patients underwent implantation of either a BVP or LBBAP based on operator preference and the clinical practice at that institution. All patients provided written, informed consent for the procedures, which included a discussion that LBBAP is a nonstandard approach to achieve cardiac resynchronization. The institutional review boards approved the retrospective observational study and data analysis at each site.

Coronary venous pacing leads were implanted in a standard fashion using quadripolar leads and targeting posterior lateral or lateral branches of the coronary venous system when possible. LBBAP was performed using previously described methods.[7] Final position of the LBBAP lead was considered successful if the unipolar paced QRS morphology demonstrated a Qr or qR pattern in V_1 along with any of the following: (1) recording of left bundle branch potential, (2) demonstration of transition from nonselective to selective left bundle branch/left ventricular (LV) septal capture during threshold testing, or (3) R-wave peak time in leads V_5 through V_6 <90 ms. In some patients, an LV lead was also implanted in a coronary venous branch at the operator's discretion to achieve LBBAP-optimized CRT (LOT-CRT) or to be available as a back-up lead.[8] Patients with LOT-CRT were included in the LBBAP group for all analysis as in the original study.

Patients had baseline demographics, medications, and ECG and echocardiogram findings recorded; they were then followed at regular intervals in the device clinic and through remote device monitoring. Devices were programmed to achieve the narrowest QRS possible by using atrioventricular delay optimization algorithms. In patients with a CRT device with right ventricular and LBBAP lead, LV-right ventricle offset was maximized (80–100 ms) or programmed to LV-only pacing to allow for LBBAP only; whereas in BVP cases, the LV-right ventricle offset was adjusted appropriately to allow for the narrowest paced QRS duration, including the use of "adaptive" LV-only

pacing or similar algorithms. In some patients receiving LBBAP and LV leads, LBBAP-LV timing was optimized to achieve the narrowest QRS (LOT-CRT) in patients with intraventricular conduction delay or incomplete electrical resynchronization by LBBAP.[8] In some of these patients, an LV lead was used as backup (LBBAP-LV offset programmed to 80–100 ms or LV lead turned off). Ventricular pacing percentage was routinely documented in all patients. Information regarding the occurrence of arrhythmias was obtained from inpatient and outpatient records and device interrogations. Echocardiographic response was defined as a ≥5% increase in LVEF. Hyperresponder status was defined as an absolute improvement in LVEF by ≥20% or improvement of LVEF to >50%.

The individual primary end points were time to sustained ventricular tachycardia or ventricular fibrillation (VT/VF) and new-onset AF (lasting >30 s) among propensity score–matched patients undergoing BVP compared with LBBAP.

The secondary end points comprised the overall incidence of ventricular arrhythmias, including: nonsustained VT (≥10 beats at ≥150 bpm); antitachycardia pacing; ICD shocks; VT storm; VT ablation; duration of AF lasting >30 s, >6 minutes, and >24 hours; cardioversion; AF ablation; and atrioventricular node ablation.

Statistical Analysis

All data were summarized as frequencies and percentages for categorical data and means±SDs for continuous data. Comparison between the groups was accomplished with the use of χ^2 or Fisher exact test and independent sample *t* test or Mann-Whiteny *U* test as appropriate.

To adjust for bias due to potential confounders, a propensity score (PS) matching approach was performed to match participants in BVP and LBBAP groups at a ratio of 1:1. In particular, potential confounding factors, including age, sex, diabetes, hypertension, body mass index, coronary artery disease, ischemic cardiomyopathy, left bundle branch block (LBBB), baseline QRS duration, LVEF, LV end-diastolic diameter, QRS morphology, New York Heart Association functional class, and medication use for HF and amiodarone, were fit into a multivariable logistic model with a caliper set at 0.05. Cox proportional hazard ratios (HRs) were used to estimate survival probability for the individual end points with adjustment for potential confounders, specifically with reference to the 15 participating centers. A survival analysis of time to sustained VT/VF was evaluated separately in patients without previous sustained VT/VF or amiodarone therapy. A survival analysis was also performed among patients with echocardiographic response and nonresponders. All data and follow-up dates were censored after December 31, 2022. For the Cox proportional hazard time-to-event analysis, time censoring was determined by time to event or time to last follow-up, whichever came first. Statistical analysis was performed using SPSS software version 29 (IBM Corp, Armonk, NY).

RESULTS

Baseline Characteristics

A total of 1778 patients who had successful implantation of a CRT device using BVP or LBBAP were followed for a mean duration of 25.2±15.6 months. Among these patients, PS matched 707 patients with BVP to 707 patients with LBBAP (n=1414). The baseline characteristics of the entire study population and PS-matched cohort are shown in Table 1. The baseline characteristics of the patients in this PS-matched cohort were similar, including sex, ischemic cardiomyopathy, LBBB, or amiodarone therapy. The baseline characteristics of patients without a history of AF among the PS-matched cohort (n=890) are shown in Table 2. The baseline characteristics in this subgroup were well-matched except for a slightly higher left ventricular end-diastolic diameter in the BVP group.

End Point Analysis

Ventricular Arrhythmias

The primary end point of time to sustained VT or ventricular fibrillation (VT/VF) occurred in 6.8% of all patients (96/1414; Tables 3 through 5). Sustained VT/VF occurred in 4.2% (30/707) of patients with LBBAP compared with 9.3% (66/707) of patients with BVP (HR, 0.46 [95% CI, 0.29–0.74]; *P*<0.001). Cox proportional hazards time-to-event curves are shown in Figure 1. The secondary end point of overall incidence of ventricular tachyarrhythmias (VTA, including nonsustained VT, sustained VT, and VF) was observed in 11.5% of all patients (162/1414) and was reached in 7.8% of patients with LBBAP (55/707) compared with 15.1% of patients with BVP (107/707; *P*<0.001; Tables 3 through 5). VT storm was less frequent with LBBAP than with BVP (0.8% versus 2.5%; *P*=0.013). Antitachycardia pacing occurred in 4.7% of patients (66/1414) and was similar with LBBAP (3.7%) compared with BVP (5.7%; *P*=0.08). ICD shocks occurred in 5.2% of patients (74/1414) and were less frequent among patients with LBBAP (3.3%) compared with BVP (7.2%; *P*<0.001). The incidence of VT ablation did not differ between groups. In the PS-matched group, there were no significant differences in the prevalence of preexisting sustained VT/VF (6.5% versus 8.8%; *P*=0.07; Tables 3 through 5) or amiodarone therapy (14.4% versus 15.8%; *P*=0.46; Table 1) between patients in the LBBAP group and the BVP group.

ICD Versus Pacemaker

In our study PS cohort of 1414 patients, 79% (1115/1414) received an ICD and 21% (299/1414) received a pacemaker (Tables 6 and 7). Patients who received an ICD more frequently had ischemic cardiomyopathy (38% versus 25%; *P*<0.01) and had a lower LVEF (26±6% versus 29±6%; *P*<0.01; Tables 6 and 7). The incidence of sustained VT/VF was observed in 7.9% of patients (88/1115) with ICD compared with 2.7% of patients (8/299) with pacemaker (*P*<0.001; Tables 6 and 7). The incidence of sustained VT/VF was less frequent among patients undergoing LBBAP compared with BVP in both patients with ICD and pacemaker (*P*=0.015 and

Table 1. Baseline Characteristics of All Patients and Propensity Score–Matched Cohort

Baseline characteristics	All patients				Propensity score–matched patients			
	All patients (n=1778)	BVP (n=981)	LBBAP (n= 797)	*P* value	PS-All patients (n=1414)	PS-BVP (n=707)	PS-LBBAP (n=707)	*P* value
Age, y	69±12	68±12	69±12	0.33	69.5±12	69.0±12	69.9±12	0.12
Female, n (%)	575 (32)	294 (30)	281 (36)	0.02	472 (33.4)	239 (33.8)	233 (33.0)	0.74
Hypertension, n (%)	1145 (64)	614 (63)	529 (66)	0.12	952 (67.3)	461 (65.2)	491 (69.4)	0.09
Diabetes, n (%)	698 (39)	381 (39)	317 (40)	0.69	567 (40)	286 (40.5)	281 (39.7)	0.79
Coronary artery disease, n (%)	858 (48)	480 (49)	378 (47)	0.488	683 (48.3)	338 (47.8	345 (48.8)	0.71
Atrial fibrillation, n (%)	650 (37)	364 (37)	286 (36)	0.14	524 (37.1)	253 (35.8)	271 (38.3)	0.32
Body mass index, kg/m^2	28±6	28.8±6.8	27.5±6	<0.01	27.9±5	28.1±5.8	27.8±5.0	0.18
Type of cardiomyopathy, n (%)				<0.01				0.85
Ischemic	649 (36)	386 (39)	263 (33)		501 (35.4)	251 (35.5)	250 (35.4)	
Nonischemic	1029 (58)	550 (56)	479 (60)		830 (58.7)	417 (59.0)	413 (58.4)	
Mixed	100 (6)	45 (5)	55 (7)		83 (5.9)	39 (5.5)	44 (6.2)	
New York Heart Association class	2.7±0.6	2.7±0.6	2.8±0.6	<0.01	2.7±0.7	2.7±0.7	2.7±0.7	0.91
Ejection fraction, %	27±6	26±6	27±6	<0.01	26.3±6	26.2±6	26.5±6	0.31
Left ventricular end-diastolic diameter, mm	61±9	62±9	60±9	<0.01	60.8±8	61.1±8	60.5±8	0.17
Baseline QRS, ms	160±26	160±24	160±28	0.63	161±26	161±25	161±28	0.78
QRS morphology, n (%)				<0.01				0.42
Left bundle branch block	1073 (61)	626 (64)	447 (56)		816 (57.7)	419 (59.3)	397 (56.2)	
Right bundle branch block	173 (10)	96 (10)	77 (10)		144 (10.2)	77 (10.9)	67 (9.5)	
Intraventricular conduction delay	153 (9)	76 (8)	77 (10)		137 (9.7)	61 (8.6)	53 (10.7)	
Normal	127 (7)	57 (6)	70 (9)		103 (7.3)	50 (7.1)	53 (7.5)	
Right ventricular pacing	248 (14)	126 (13)	126 (16)		214 (15.1)	100 (14.1)	114 (16.1)	
Ventricular pacing percentage	96±10	96±9	95±13	0.17	95.7±11	96.2±9	95.2±13	0.10
Beta-blockers	1587 (89)	871 (89)	716 (90)	0.48	1258 (89)	632 (89.4)	626 (88.5)	0.61
Angiotensin converting enzyme inhibitor/ angiotensin receptor blocker	737 (42)	412 (42)	325 (41)	0.6	592 (41.9)	293 (41.4)	299 (42.3)	0.75
Angiotensin receptor neprilysin inhibitor	683 (38)	384 (39)	299 (38)	0.47	525 (37.1)	267 (37.8)	258 (36.5)	0.62
Aldosterone antagonists	966 (54)	537 (55)	429 (54)	0.7	748 (52.9)	372 (52.6)	376 (53.2)	0.83
Diuretics	1325 (74)	706 (72)	619 (78)	<0.01	1072 (75.8)	542 (76.7)	530 (75)	0.46
Amiodarone	279 (15)	173 (18)	106 (13)	0.01	214 (15.1)	112 (15.8)	102 (14.4)	0.46

BVP indicates biventricular pacing; LBBAP, left bundle branch area pacing; and PS, propensity score matched.

P<0.001, respectively; Tables 6 and 7). As a result, the incidence of ICD therapies, in particular, ICD shocks, was lower among patients with LBBAP compared with BVP. Of the 8 patients with BVP pacemakers who developed sustained VT/VF, 6 underwent an upgrade to a BVP-ICD device. One older patient with a well-tolerated slow VT that responded to oral amiodarone elected not to undergo ICD upgrade. Another patient presenting in VT storm was treated with intravenous amiodarone and lidocaine and died after a long hospitalization before undergoing an ICD upgrade. The secondary end point of the overall incidence of VTA (including nonsustained VT and sustained VT/VF) was observed in 12.6% of patients (140/1115) with an ICD compared with 7.4% of patients (22/299) with a pacemaker (*P*<0.01). The incidence of VT storm was 2.2% in patients (24/1115) with an ICD and none in patients with a pacemaker (*P*=0.01). An ablation procedure for VT was performed in 1.6% of patients (18/1115) with an ICD compared with none of the patients with a pacemaker (*P*<0.05). The incidence of VT storm or VT ablation did not differ between patients undergoing LBBAP versus BVP. Patients undergoing LOT-CRT were analyzed as part of the LBBAP group and, when excluded from LBBAP (n=65), the incidence of sustained VT/VF was significantly lower in the LBBAP group than in the BVP group (3.5% versus 9.3%; HR, 0.36 [95% CI, 0.19–0.76]; *P*<0.001). In addition, when the primary outcome was analyzed incorporating the 15 implanting centers as a stratification variable in the Cox proportional hazard survival model, the difference between BVP and LBBAP

Table 2. Baseline Characteristics of Patients Without a History of Atrial Fibrillation (AF) Among Propensity Score–Matched Cohort

Baseline characteristics	Patients without a history of AF			
	All patients (n=890)	Biventricular pacing (n=454)	Left bundle branch area pacing (n=436)	*P* value
Age, y	66.9±13			0.90
Female, n (%)	307 (34.5)	163 (35.9)	144 (33)	0.37
Hypertension, n (%)	563 (63.3)	282 (50.1)	281 (64.4)	0.47
Diabetes, n (%)	344 (38.7)	180 (39.6)	164 (37.6)	0.53
Coronary artery disease, n (%)	425 (47.8)	218 (48)	207 (47.5)	0.87
Body mass index, kg/m^2	28±5	28±6	27±5	0.10
Type of cardiomyopathy, n (%)y				0.17
Ischemic	319 (35.8)	174 (38.3)	145 (33.3)	
Nonischemic	530 (59.6)	263 (57.9)	267 (61.2)	
Mixed	41 (4.6)	17 (3.7)	24 (5.5)	
New York Heart Association class	2.7±0.7	2.7±0.7	2.7±0.7	0.60
Ejection fraction, %	26.4±6.5	26.2±6.5	26.7±6.4	0.23
Left ventricular end-diastolic diameter, mm	61±8	62±8	61±8	0.03
Baseline QRS, ms	164±24	163±23	165±25	0.39
QRS morphology, n (%)				0.50
Left bundle branch block	591 (66.4)	295 (49.9)	296 (50.1)	
Right bundle branch block	87 (9.8)	45 (9.9)	42 (9.6)	
Intraventricular conduction delay	86 (9.7)	46 (10.1)	40 (9.2)	
Normal	27 (3)	11 (2.4)	16 (3.7)	
Right ventricular pacing	99 (11.1)	57 (12.6)	42 (9.6)	
Ventricular pacing percentage	97±8	97±8	97±8	0.55
Medications, n (%)				
Beta-blockers	809 (90.9)	408 (89.9)	401 (92)	0.28
Angiotensin converting enzyme inhibitor/ angiotensin receptor blocker	380 (42.7)	186 (41)	194 (44.5)	0.29
Angiotensin receptor neprilysin inhibitor	362 (40.7)	194 (42.7)	168 (38.5)	0.20
Aldosterone antagonists	505 (56.7)	251 (55.3)	254 (58.3)	0.37
Diuretics	672 (75.5)	347 (76.4)	325 (74.5)	0.51
Amiodarone	102 (11.5)	58 (12.8)	44 (10.1)	0.21

remained significant while the potential confounder, "implanting centers," was not significant (*P*=0.35).

Among 1139 (81%) patients with follow-up echocardiograms, echocardiographic response defined as improvement in LVEF ≥5% was observed in 68% (n=770; BVP 64% versus LBBAP 71%; *P*=0.02) of patients. The incidence of sustained VT/VF was significantly lower among responders compared with nonresponders (4.8% versus 11.4%; *P*<0.001). Among the responders, the incidence of sustained VT/VF was lower in LBBAP compared with BVP (2.7% versus 7.3%; HR, 0.33 [95% CI, 0.15–0.74]; *P*=0.007). Among the nonresponders, there was no significant difference in the incidence of sustained VT/VF between LBBAP and BVP (7.2% versus 14.8%; HR, 0.51 [95% CI, 0.25–1.06]; *P*=0.07; Figure S1). Echocardiographic hyperresponse, defined as improvement in LVEF ≥20% or normalization of LVEF to ≥50%, was observed in 27% (n=308; LBBAP 29% versus BVP 25%; *P*=0.06) of patients. The incidence of sustained VT/VF was significantly lower among those with hyperresponse compared with others (3.2% versus 8.3%; *P*=0.004).

Ventricular Arrhythmias in Patients Without a History of VT/VF or Antiarrhythmic Therapy

There were no differences in the baseline characteristics of patients with no history of VT/VF or antiarrhythmic therapy (n=1194; Table S1). Amiodarone was used for management of AF and ventricular tachyarrhythmias in the study population. The primary end point of sustained VT/VF in patients without previous VT/VF and antiarrhythmic therapy occurred in 3.2% (19/603) of

Table 3. Ventricular Tachyarrhythmias in All Patients

Ventricular tachyarrhythmias in all patients	PS-All patients (n=1414)	PS-BVP (n=707)	PS-LBBAP (n=707)	*P* value
Ventricular arrhythmias (NSVT, VT, VF), n (%)	162 (11.5)	107 (15.1)	55 (7.8)	<0.001
Sustained VT/VF, n (%)	96 (6.8)	66 (9.3)	30 (4.2)	<0.001
Antitachycardia pacing	66 (4.7)	40 (5.7)	26 (3.7)	0.08
Implantable cardioverter defibrillator shocks	74 (5.2)	51 (7.2)	23 (3.3)	<0.001
VT storm, n (%)	24 (1.7)	18 (2.5)	6 (0.8)	0.013
VT ablation, n (%)	18 (1.3)	10 (1.4)	8 (1.1)	0.64
History of sustained VT/VF or antiarrhythmic therapy, n (%)	220 (15.6)	116 (16.4)	104 (14.7)	0.32
History of sustained VT/VF	108 (7.6)	62 (8.8)	46 (6.5)	0.07

BVP indicates biventricular pacing; LBBAP, left bundle branch area pacing; NSVT, nonsustained ventricular tachycardia; PS, propensity score matched; VF, ventricular fibrillation; and VT, ventricular tachycardia.

patients with LBBAP compared with 7.3% (43/591) of patients with BVP (HR, 0.46 [95% CI, 0.26–0.81]; *P*=0.007). Cox proportional hazards curves are shown in Figure 2. The secondary end point of overall incidence of VTA (including nonsustained VT, sustained VT/VF) was reached in 9.9% of patients (118/1194) without previous VT/VF and antiarrhythmic therapy and was observed in 6.6% of patients with LBBAP (40/603) compared with 13.2% of patients with BVP (78/591; *P*=0.003; Tables 3 through 5). VT storm was less frequent with LBBAP compared with BVP (0.2% versus 1.3%; *P*=0.02). Antitachycardia pacing occurred in 3.6% of all patients (43/1194) and occurred in 2.8% with LBBAP compared with 4.4% with BVP (*P*=0.15). ICD shocks occurred in 3.9% of all patients (46/1194) and occurred in 2.2% with LBBAP compared with 5.6% of patients with BVP (*P*=0.002; Tables 3 through 5). The rate of VT ablation did not differ between the 2 groups.

New-Onset AF

The primary end point of new-onset AF was analyzed among the propensity-matched cohort in a prespecified subgroup of patients without a history of AF (n=890) and occurred in 4.7% of patients. New-onset AF occurred in 2.8% (12/436) of patients with LBBAP compared with 6.6% (30/454) of patients with BVP (HR, 0.34 [95% CI, 0.16–0.73]; *P*=0.008). Cox proportional hazards time-to-event curves are shown in Figure 3. The secondary end points of AF >6 minutes and AF >24 hours were less frequent in patients with LBBAP than in patients with BVP (1.8% versus 5.1%, *P*=0.02 and 0.7% versus 2.9%, *P*=0.015, respectively; Tables 3 through 5). There was no difference in the incidence of AF therapies (cardioversion, AF ablation, and atrioventricular junction ablation) in patients with LBBAP compared with BVP.

DISCUSSION

This large international, multicenter, retrospective, observational study shows a decreased incidence of ventricular arrhythmias as well as new-onset AF in patients undergoing CRT by LBBAP compared with BVP. The lower incidence of sustained VT/VF in the LBBAP group translated into a substantial reduction in ICD therapies. The incidence of nonsustained VT and VT storm was similarly decreased in the patients with LBBAP versus BVP. The incidence of AF lasting >30 s, >6 minutes, or >24 hours was also reduced in patients undergoing LBBAP compared with BVP. These observations suggest that physiological pacing and more effective CRT by LBBAP may promote remodeling that provides a less arrhythmogenic substrate compared with BVP.

Incidence of Sustained VT/VF in BVP CRT Trials

In MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy), a conventional CRT ICD was associated with a 29%

Table 4. Ventricular Tachyarrhythmias in Patients Without Previous VT/VF or Antiarrhythmic Therapy

Ventricular tachyarrhythmias in patients with no previous VT/VF or antiarrhythmic therapy	PS-All patients (n=1194)	PS-BVP (n=591)	PS-LBBAP (n=603)	*P* value
Ventricular arrhythmias (NSVT, VT, VF), n (%)	118 (9.9)	78 (13.2)	40 (6.6)	0.003
Sustained VT/VF, n (%)	62 (5.2)	43 (7.3)	19 (3.2)	0.001
Antitachycardia pacing	43 (3.6)	26 (4.4)	17 (2.8)	0.15
Implantable cardioverter defibrillator shocks	46 (3.9)	33 (5.6)	13 (2.2)	0.002
VT storm, n (%)	9 (0.8)	8 (1.3)	1 (0.2)	0.02
VT ablation, n (%)	8 (0.7)	3 (0.5)	5 (0.9)	0.49

AF, atrial fibrillation; BVP, biventricular pacing; LBBAP, left bundle branch area pacing; NSVT, nonsustained ventricular tachycardia; PS, propensity score matched; VF, ventricular fibrillation; and VT, ventricular tachycardia.

Table 5. Atrial Fibrillation in Patients Without Prior History of AF

AF in patients with no previous AF	PS-All patients (n=890)	PS-BVP (n=454)	PS-LBBAP (n=436)	*P* value
New-onset AF (>30 s), n (%)	42 (4.7)	30 (6.6)	12 (2.8)	0.007
AF >6 min	31 (3.5)	23 (5.1)	8 (1.8)	0.02
AF >24 h	16 (1.8)	13 (2.9)	3 (0.7)	0.015
Electrical cardioversion	4 (0.4)	3 (0.7)	1 (0.2)	0.34
AF ablation, n (%)	2 (0.2)	2 (0.4)	0 (0)	0.17
Atrioventricular node ablation, n (%)	2 (0.2)	2 (0.4)	0 (0)	0.17

AF indicates atrial fibrillation; BVP, biventricular pacing; LBBAP, left bundle branch area pacing; and PS, propensity score matched.

reduction in the risk of a first life-threatening VTA (*P*=0.003) compared with ICD therapy alone.[9] In patients with baseline LBBB, risk reduction was 42% compared with no risk reduction in patients without LBBB.[9] Recurrent VTA was associated with higher risk of subsequent HF or death.

In a reanalysis of MADIT-CRT limited to patients with LBBB and HF, CRT ICD was associated with a risk reduction of 32% for VTA recurrence, 57% for recurrent life-threatening VTA, 54% for appropriate ICD shocks, and 25% for the combined end point of VTA and death.[10] Subgroup analysis showed that risk reduction was more pronounced among those in New York Heart Association functional class I (68%) than among those in New York Heart Association functional class II (24%).[10] Improved LVEF and LV dimensions were associated with a lower risk and ischemic cardiomyopathy with higher risk of VTA.[10]

The REVERSE study (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) was a multicenter randomized, double-blind trial of 508 patients with mild systolic HF undergoing BVP.[11] The study randomly assigned patients to CRT ON versus OFF. There were no differences in VTA episodes or VT storm between groups. The event rate was similar in the CRT ON and OFF groups (19% versus 22%). The incidence of VTA was reduced in patients with reverse remodeling compared with those without reverse remodeling (5.6% versus 16.3%). The REVERSE study was also the first randomized study to show less VTA in women with BVP.[11]

The effect of BVP on VTA incidence is controversial. A combined analysis of CONTAK-CD and InSync-ICD trials failed to show a reduction of VTA episodes in patients undergoing BVP compared with ICD therapy alone.[12] These observations were further supported by negative findings from the REVERSE, InSync-ICD, and the RAFT (Resynchronization in Ambulatory Heart Failure) trials.[11,13] All of these trials included patients without LBBB.[14–17] In contrast, several small studies showed a reduction of VTA frequency with CRT ICD therapy.[18–21] Ermis et al[18] demonstrated reduced VTA burden and frequency of ICD shocks among 18 patients after upgrade to CRT-D. Voigt et al[20] showed similar results among 19 patients, demonstrating a potential benefit of CRT by BVP on reducing VTA burden.

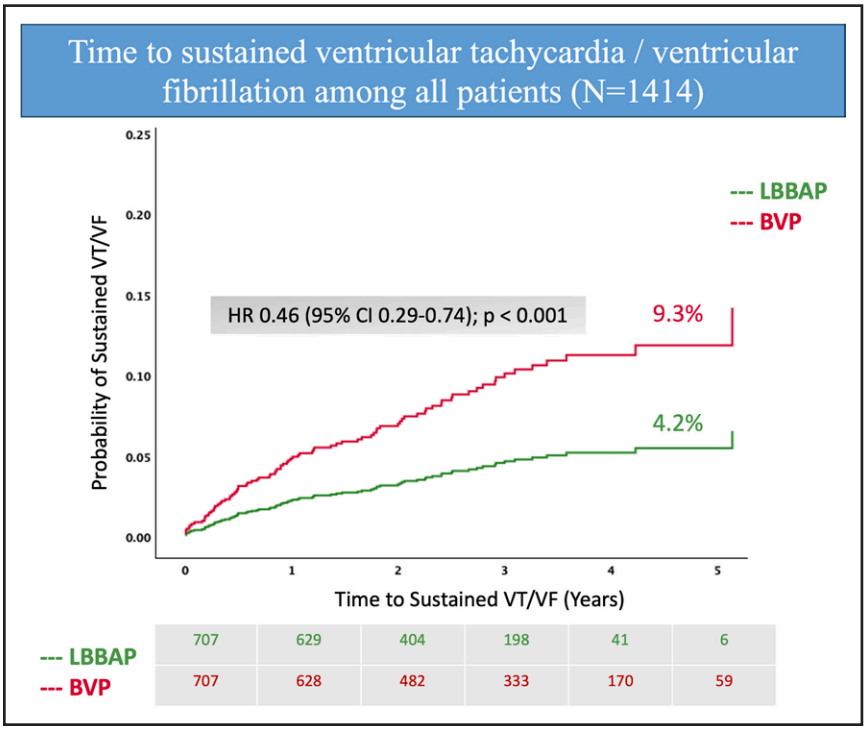

Figure 1. Sustained VT/VF.
Left bundle branch area pacing (LBBAP) was associated with a lower incidence of sustained VT/VF in patients undergoing cardiac resynchronization therapy compared with biventricular pacing (BVP). HR indicates hazard ratio; VF, ventricular fibrillation; and VT, ventricular tachycardia.

Table 6. Ventricular Arrhythmias and VT Therapy in Patients with ICDs

Patients with ICDs (n=1115)	All patients (n=1115)	BVP (n=596)	LBBAP (n=519)	*P* value
Ischemic cardiomyopathy, n (%)	425 (38)	225 (38)	200 (39)	0.79
Left ventricular ejection fraction, %	26±6	26±6	26±6	0.90
Left bundle branch block, n (%)	642 (58)	358 (60)	284 (55)	0.72
QRS duration, ms	161±26	160±26	161±27	0.60
Ventricular arrhythmias (NSVT, VT, VF), n (%)	140 (12.6)	91 (15.3)	49 (9.4)	<0.01
Sustained VT/VF, n (%)	88 (7.9)	58 (9.7)	30 (5.8)	0.015
Antitachycardia pacing	60 (5.4)	34 (5.7)	26 (5.0)	0.61
ICD shocks	70 (6.3)	47 (7.9)	23 (4.4)	0.018
VT storm, n (%)	24 (2.2)	18 (3.0)	6 (1.2)	0.032
VT ablation, n (%)	18 (1.6)	10 (1.7)	8 (1.5)	0.86

BVP indicates biventricular pacing; ICD, implantable cardioverter defibrillator; LBBAP, left bundle branch area pacing; NSVT, nonsustained ventricular tachycardia; VF, ventricular fibrillation; and VT, ventricular tachycardia.

Proarrhythmia Encountered in Patients With BVP

There have been numerous reports of VT storm after BVP initiation, raising concerns related to proarrhythmia.[16,22–26] The incidence of VT storm after the initiation of BVP was studied prospectively in 191 patients undergoing implantation of a BVP defibrillator.[26] VT storm occurred in 8 of 191 patients (4%) and was characterized by recurrent sustained monomorphic VT with a single morphology.[26] All patients with VT storm were men (7 with ischemic heart disease) with a remote (5±2 years) history of VT. VT storm developed a mean of 16±12 days after initiation of BVP. VT storm was refractory to intravenous antiarrhythmics and was managed by turning off LV pacing and catheter ablation and long-term oral antiarrhythmic therapy. Presenting with VT storm carried a poor prognosis.[26]

Fish et al[15] demonstrated that reversal of the direction of activation of the LV wall, as occurs during BVP, leads to a prominent increase in QT and transmural dispersion of repolarization as a result of earlier repolarization of epicardium and delayed activation and repolarization of the midmyocardial M cells. Increased transmural dispersion of repolarization may create the substrate for the development of torsade de pointes, and other re-entrant arrhythmias under long QT conditions.[14,15] Furthermore, BVP associated with colliding wavefronts in proximity or within myocardial scar and regions of slow conduction may increase the likelihood of VTA. Roque et al[27] performed VT ablation procedures in 8 patients with ventricular proarrhythmia after the initiation of BVP presenting in VT storm that improved after the discontinuation of LV pacing.[27] In all 8 patients, the LV lead was positioned within epicardial scar close to the VT substrate. Catheter ablation allowed for resumption of BVP in all patients.

The causes(s) for proarrhythmogenicity of cardiac stimulation are multiple. Chronic endocardial right ventricular pacing is an independent predictor of sustained VT/VF in patients with HF, likely driven primarily by pacing-induced cardiomyopathy.[28,29] Furthermore, there is evidence that CRT by BVP may ameliorate VTA in patients with HF if there is evidence of LV remodeling.[11,17,18,30] A carefully performed meta-analysis of 23 studies involving patients with an ICD compared the incidence of VTA in CRT responders, CRT nonresponders, and ICD-only patients.[17] CRT responders were less likely to experience VTA than CRT nonresponders as well as patients with ICD only. Patients with ICD only had a lower likelihood of VTA compared with CRT nonresponders.[17] Hence, although CRT is antiarrhythmic after LV reverse remodeling, it can also be potentially proarrhythmic in its absence. In our study, patients with echocardiographic response and hyperresponse had significantly lower incidence of sustained VT/VF than echocardiographic nonresponders.

Conduction system pacing establishes normal or close to normal ventricular activation, referred to as physiological pacing, and is frequently associated with cardiac memory, and the associated T-wave changes will normalize within weeks after correction of abnormal ventricular activation.[31] We have reported the use of permanent His-bundle pacing to manage ventricular

Table 7. Ventricular Arrhythmias and VT Therapy in Patients with Pacemakers

Patients with pacemakers (n=299)	All patients (n=299)	BVP (n=111)	LBBAP (n=188)	*P* value
Ischemic cardiomyopathy, n (%)	76 (25)†	26 (23)†	50 (27)†	0.54
Left ventricular ejection fraction, %	29±6‡	29±6‡	29±6‡	0.13
Left bundle branch block, n (%)	174 (58)	61 (55)	113 (60)	0.38
QRS duration, ms	162±30	164±26	161±31	0.03
Ventricular arrhythmias (NSVT, VT, VF) , n (%)	22 (7.4)	16 (14.4)	6 (3.2)	<0.001
Sustained VT/VF, n (%)	8 (2.7)	8 (7.2)	0 (0)	<0.001
Antitachycardia pacing*	6 (2)	6 (5.4)	0 (0)	0.001
ICD shocks*	4 (1.3)	4 (3.6)	0 (0)	0.009
VT storm	0	0	0	
VT ablation	0	0	0	

BVP indicates biventricular pacing; ICD, implantable cardioverter defibrillator; LBBAP, left bundle branch area pacing; NSVT, nonsustained ventricular tachycardia; VF, ventricular fibrillation; and VT, ventricular tachycardia.

*Among 8 patients with BVP pacemakers and sustained VT/VF, 6 underwent an upgrade to a BVP-ICD.

†*P*<0.01 compared with patients with ICD.

‡*P*<0.001 compared with patients with ICD

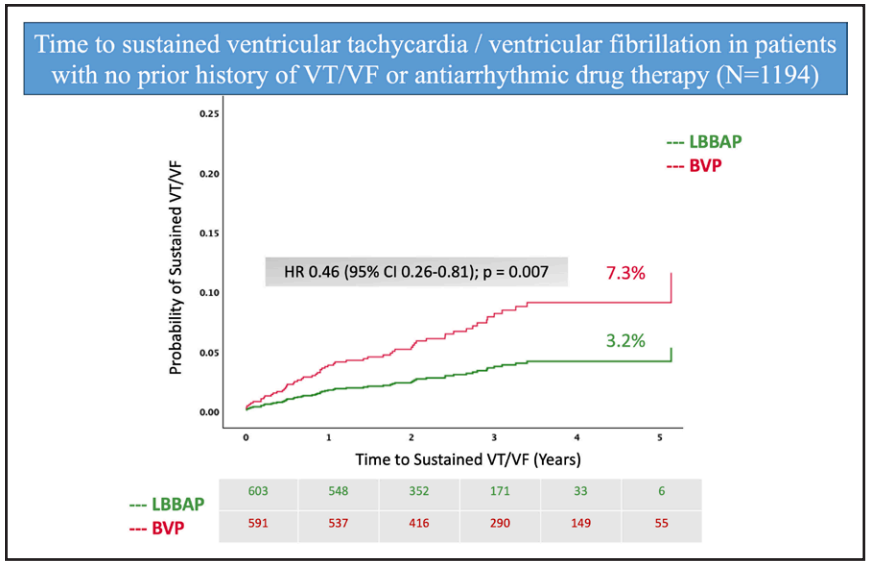

Figure 2. Sustained VT/VF in patients with no history of VT/VF or antiarrhythmic drug therapy. Left bundle branch area pacing (LBBAP) was associated with a lower incidence of sustained VT/VF compared with biventricular pacing (BVP) in this subgroup of patients. HR indicates hazard ratio; VF, ventricular fibrillation; and VT, ventricular tachycardia.

proarrhythmia that developed after initiation of BVP and was unresponsive to antiarrhythmic and ablative therapy.[5] Whether conduction system pacing can be reliably used to treat patients with proarrhythmia due to BVP or VTA, in general, remains to be investigated. On rare occasions even conduction system pacing may be associated with proarrhythmia.[32]

Incidence of New-Onset AF With BVP

Data from randomized trials have suggested a modest or no effect of BVP on the incidence of AF. Borleffs et al[33] studied the incidence of new-onset AF in 223 patients undergoing CRT by BVP. Fifty-five (25%) patients developed new-onset AF during a follow-up of 32±16 months. Patients with AF showed less LV reverse remodeling and less improvement in LV function compared with patients without AF. Patients with AF experienced more appropriate ICD shocks for VTA, more inappropriate shocks, and more HF hospitalizations than patients without AF.[33]

In the CARE-HF trial (Cardiac Resynchronisation in Heart Failure), 813 patients with HF were randomly assigned to pharmacological therapy alone or BVP.[34] During a follow-up of 29 months, AF had been documented in 16% of patients undergoing CRT compared with 14% who received medical therapy only. There was no difference

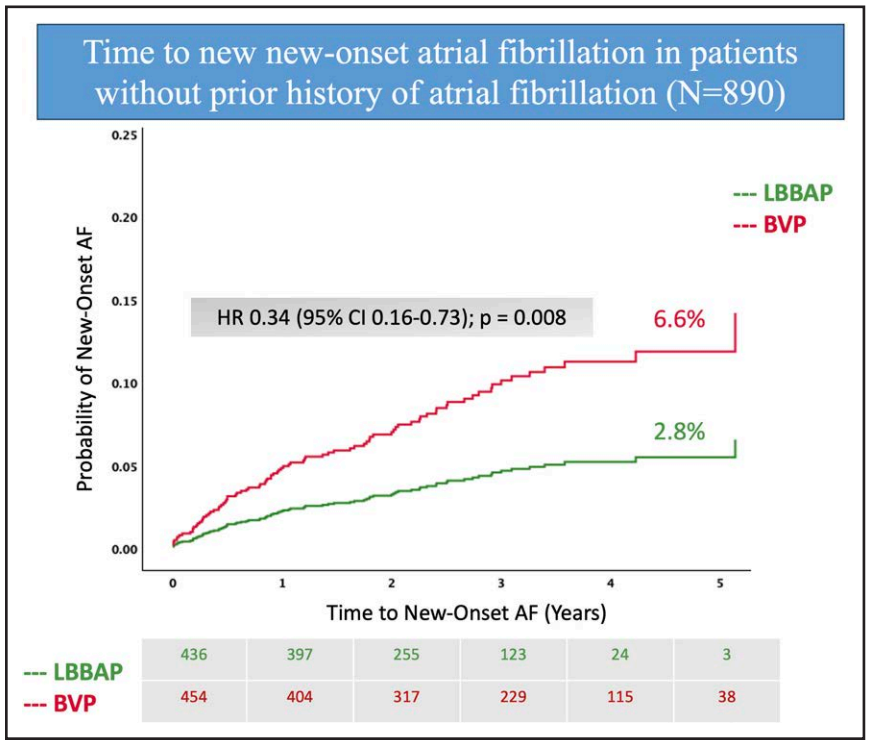

Figure 3. New-onset atrial fibrillation. Left bundle branch area pacing (LBBAP) was associated with lower incidence of new-onset AF compared with biventricular pacing (BVP) in patients without a history of atrial fibrillation (AF). HR indicates hazard ratio.

in the time to first onset of AF between groups. Mortality was higher in patients who developed AF.[34]

AdaptivCRT (aCRT, Medtronic, Mounds View, MN) is a device-based algorithm for synchronized LV pacing and continuous optimization of CRT.[35,36] The adaptive CRT trial (Adaptive Cardiac Resynchronization Therapy Study [aCRT]) randomly assigned patients to adaptive versus conventional BVP. During follow-up (20.2±5.9 months), AF >48 hours occurred in 8.7% of patients with adaptive CRT and 16.2% with conventional CRT ($P<0.03$).[35] Better optimized CRT may reduce the incidence of AF. In several studies evaluating response to BVP echocardiographically by improved interatrial conduction, left atrial emptying fraction and strain, patients with improved atrial physiology had a decreased incidence of new-onset AF.[37–39]

In summary, the data on BVP suggest at the most a modest effect of BVP on the incidence of new-onset AF limited mainly to CRT responders.[40] The data in the era of conduction system pacing appear to be more encouraging. Zhu et al[41] prospectively studied new-onset AF in a cohort of 527 patients undergoing either LBBAP (n=270) or right ventricular pacing (n=257). During a follow-up of 11 months, LBBAP resulted in a lower incidence of new-onset AF compared with right ventricle pacing (7.4% versus 17.0%; $P<0.001$) and AF burden, respectively (3.7±1.9% versus 9.3±2.2%; $P<0.001$). After adjusting for confounding factors the difference in AF incidence and burden between groups persisted.

An observational study by Ravi et al[42] reported on 410 patients with pacemakers (173 with LBBAP and 237 with right ventricular pacing) followed for 600±278 days. A new diagnosis of AF ≥30 s was noted in 5% patients in the LBBAP group and 18% patients in the right ventricular pacing group. Multivariable analysis revealed that LBBAP was associated with a lower risk of AF ≥30 s ($P=0.002$) and new-onset AF ≥6 minutes ($P=0.05$) in all patients and in the subgroup of patients with ventricular pacing burden ≥20%.

These data are in accord with the observations made in our large observational cohort of patients with HF. After excluding patients with a history of AF, we observed a lower incidence of new-onset AF. This observation is likely explained by the more complete resynchronization by LBBAP reported previously.[7] Furthermore, conduction system pacing may be associated with improved diastolic function compared with BVP.[43] More physiological LBBAP may result in decreased left atrial pressure and reverse atrial remodeling. Well-designed prospective studies among such patients, as well as among patients not meeting traditional CRT criteria, are needed.

Limitations

This was an observational, multicenter, nonrandomized, international study leading to some differences in patient populations undergoing BVP versus LBBAP. The patients underwent implantation according to operator and institutional preference. The cardiac implantable electronic device data were not analyzed by a core laboratory in a blinded fashion. Device programming (BVP modes and optimization, tachy-therapy settings, etc), follow-up, and guideline-directed medical therapy may not have been uniform across centers. Information regarding left atrial size or chronic kidney disease was not available, and differences in these confounders could have contributed to the observed differences in outcomes. In addition, due to the lack of available data, we could not use unrelated outcomes as falsification end points to reduce bias/confounders. It is likely that additional unrecognized confounders including heterogeneity among the centers and bias may have contributed to the higher incidence of arrhythmias in the BVP group, and our results should be confirmed by randomized clinical trials.

Conclusions

This large, multicenter, observational study showed that LBBAP was associated with lower incidence of sustained and nonsustained ventricular tachyarrhythmias, and new-onset AF compared with BVP. Physiological resynchronization by LBBAP may lower the risk of arrhythmias compared with BVP. Large-scale, prospective, randomized clinical trials evaluating the difference of arrhythmias in patients undergoing CRT by LBBAP and BVP are required to confirm the conclusions drawn from this study.

ARTICLE INFORMATION

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Supplemental Material

Table S1

Figure S1

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