JACC: CLINICAL ELECTROPHYSIOLOGY
VOL. ■, NO. ■, 2022

ISSN 2405-500X/$36.00
PUBLISHED BY ELSEVIER

Letters

Clinical Impacts and Insights Into Mechanisms of Paced Fragmented QRS in Cardiac Resynchronization Therapy Patients

Cardiac resynchronization therapy (CRT) is an established treatment for patients with a left ventricular (LV) dysfunction and conduction delay. Myocardial scarring can induce a conduction delay, which results in less effective CRT.[1] Fragmented QRS complex (fQRS) is associated with myocardial fibrosis and an increased risk of ventricular arrhythmias (VAs).[2] However, few published reports exist regarding patients with CRT and the direct association between fQRS and paced conduction time or myocardial scarring during ventricular pacing. Thus, we hypothesized that fQRS induced by biventricular pacing, including LV pacing, could indicate conduction abnormalities and be associated with adverse outcomes among patients with CRT. The objective of this study was to investigate the clinical impacts of fQRS during CRT pacing, as well as its direct relationship to myocardial scarring.

We investigated 162 consecutive patients with congestive heart failure (HF), despite optimal medical therapy in which data were available.[3] This study was approved by the Institutional Review Board of the National Cerebral and Cardiovascular Center, Suita, Japan (M26-150-10) and conducted in accordance with the Declaration of Helsinki.

fQRS was defined as the presence of various RSR′ patterns with or without Q wave, which include an additional R wave (R′) or notching of the R wave or notching of the S wave, or the presence of more than 2 R′s (fragmentation) in 2 contiguous leads corresponding to a major lead set, namely anterior (V_1-V_4), inferior (II, III, aVF), or lateral (I, aVL, V_5, V_6) (**Figure 1**).[4] The electrocardiogram measurements were retrospectively performed by 3 independent reviewers (N.U, T.N, and A.I) who were blinded to the clinical outcome and image data. The conduction time from LV pace to right ventricular (RV) sense (LVp-RVs) and from RV pace to LV sense (RVp-LVs) was assessed intraoperatively. The difference between LVp-RVs and RVp-LVs ([LVp-RVs] - [RVp-LVs]) was calculated.[3] Electrocardiogram-gated myocardial perfusion single-photon emission computed tomography imaging with technetium Tc 99m sestamibi was performed to measure myocardial damage to characterize perfusion defects. We evaluated the composite outcome of cardiac death and/or HF hospitalization, as well as VA. A CRT responder was defined as a patient with improved LV ejection fraction ≥10% and/or reduced LV end-systolic volume ≥15%, compared with the baseline measurements, 6 months after CRT device implantation. The results are summarized as mean ± SD. Survival curves were determined by the Kaplan-Meier method and were analyzed by the log-rank test. The threshold for statistical significance was $P < 0.05$. All analyses were performed using JMP (version 14; SAS Institute).

Patients with paced fQRS had significantly lower prevalence of CRT responder (46% vs 80%; $P < 0.0001$), higher values for LVp-RVs (157.5 ± 42.8 ms vs 125.8 ± 35.4 ms; $P < 0.0001$) and (LVp-RVs) − (RVp-LVs) (5.1 ± 36.9 ms vs −22.8 ± 49.5 ms; $P < 0.0001$) than patients without paced fQRS. Patients with paced fQRS had a higher sum rest score for electrocardiogram-gated myocardial perfusion single-photon emission computed tomography imaging (19.7 ± 13.0 vs 11.4 8 .6; $P = 0.0014$), as well as defects in the anterior (9.6 ± 8.2 vs 4.8 ± 4.1; $P = 0.0025$) and lateral regions (4.9 ± 4.1 vs 2.2 ± 3.1; $P = 0.0014$) (**Table 1**). The Kaplan-Meier analysis revealed that patients with paced fQRS had a higher risk of cardiac death and/or HF hospitalization (log-rank $P = 0.0004$), as well as a ventricular arrhythmia (log-rank $P = 0.0007$) (**Figure 1**).

This is the first study to show that the presence of paced fQRS is associated with CRT response, adverse cardiac outcomes, and VAs. Additionally, we discovered that paced fQRS is associated with lower rate of CRT response consistent with conduction disturbance

TABLE 1 Clinical Characteristics of Patients With and Without Paced fQRS

Clinical Characteristics	All (n = 162)	fQRS-Positive (n = 107)	fQRS-Negative (n = 55)	*P* Value
Age, yrs old	65.0 ± 13.2	65.7 ± 12.6	63.5 ± 14.5	0.32
Male, n (%)	124 (77)	85 (79)	39 (71)	0.23
CRT-D, n (%)	153 (94)	105 (98)	48 (87)	0.0055
Secondary prevention, n (%)	46 (28)	39 (36)	7 (13)	0.0009
Medical history				
ICM, n (%)	49 (30)	34 (32)	15 (27)	0.55
DM, n (%)	54 (33)	40 (37)	14 (25)	0.12
CKD, n (%)	64 (40)	46 (43)	18 (33)	0.20
Atrial fibrillation, n (%)	31 (19)	23 (22)	8 (15)	0.28
NYHA functional class				
II, n (%)	113 (70)	75 (70)	38 (69)	0.90
III, n (%)	32 (20)	21 (20)	11 (20)	0.95
IV, n (%)	17 (10)	11 (10)	6 (11)	0.90
Medication				
β-blockers, n (%)	135 (83)	90 (84)	45 (82)	0.71
Amiodarone, n (%)	70 (43)	52 (49)	18 (33)	0.052
LV ejection fraction (%)	27.2 ± 11.5	26.5 ± 10.1	28.5 ± 13.8	0.32
LV end systolic volume (ml)	171 ± 93	176 ± 92	160 ± 94	0.29
QRS morphology				
LBBB, n (%)	42 (26)	22 (21)	20 (36)	0.032
RBBB, n (%)	16 (10)	12 (11)	4 (7)	0.42
IVCD, n (%)	67 (41)	46 (43)	21 (38)	0.56
Pacing, n (%)	37 (23)	27 (25)	10 (18)	0.30
QRS duration (ms)	156 ± 30	159 ± 31	151 ± 29	0.14
CRT responder, n (%)	93 (57)	49 (46)	44 (80)	<0.0001
Intraprocedural electrical parameters				
LVp-RVs (ms)	146.8 ± 43.0	157.5 ± 42.8	125.8 ± 35.4	<0.0001
RVp-LVs (ms)	151.1 ± 45.4	152.4 ± 48.1	148.6 ± 39.9	0.62
(LVp-RVs) - (RVp-LVs) (ms)	−4.4 ± 43.5	5.1 ± 36.9	−22.8 ± 49.5	<0.0001
Myocardial perfusion defects score (fQRS-positive: n = 66/fQRS-negative: n = 32)				
SRS	17.0 ± 12.3	19.7 ± 13.0	11.4 ± 8.6	0.0014
Anterior	8.0 ± 7.5	9.6 ± 8.2	4.8 ± 4.1	0.0025
Lateral	4.0 ± 4.0	4.9 ± 4.1	2.2 ± 3.1	0.0014
Inferior	4.3 ± 5.3	4.6 ± 5.6	3.7 ± 4.5	0.44

CKD = chronic kidney disease; CRT = cardiac resynchronization therapy; CRT-D = cardiac resynchronization therapy defibrillator; DM = diabetes mellitus; fQRS = fragmented QRS; ICM = ischemic cardiomyopathy; IVCD = intraventricular conduction delay; LBBB = left bundle branch block; LV = left ventricular; LVp = left ventricular pace; LVs = left ventricular sense; NYHA = New York Heart Association; RBBB = right bundle branch block; RVp = right ventricular pace; RVs = right ventricular sense; SRS = sum rest score.

yet associated with poorer outcomes of VA and HF hospitalization/mortality. fQRS was associated with a myocardial scar in patients with dilated cardiomyopathy. Meanwhile, a myocardial scar in the myofibroblasts is reported to generate a slow conduction.[1] Hence, fQRS is associated with myocardial scarring and results in slow conduction. The relatively small number of patients represents the main limitation of this study. Further prospective, multicenter studies that include a larger number of patients with CRT devices are warranted to confirm our findings and the results of interventions based on the presence of paced fQRS.

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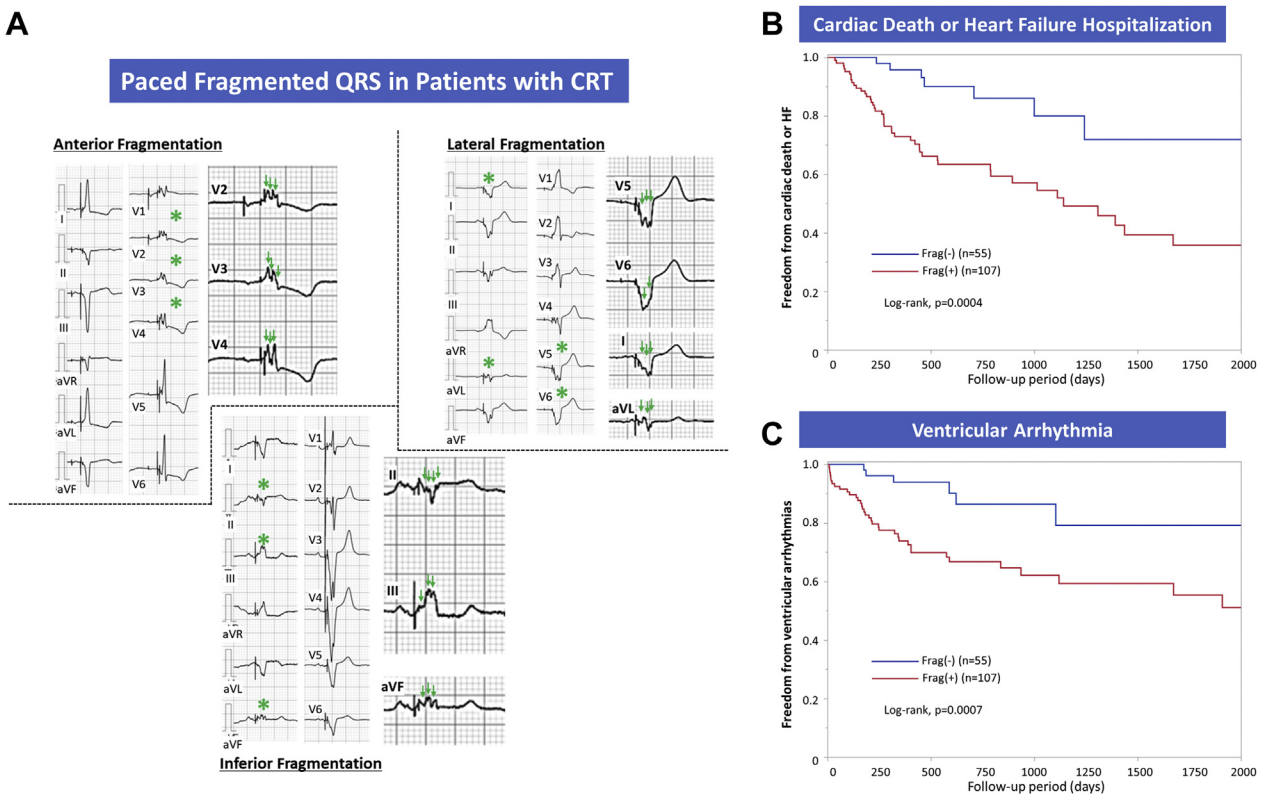
FIGURE 1 Representative ECG With Paced fQRS and Kaplan-Meier Analyses of Freedom From Cardiac Death and/or HF Hospitalization and VAs for Patients With and Without Paced fQRS



(A) A representative electrocardiogram (ECG) of anterior, lateral, and inferior fragmentation. Paced fragmented QRS (fQRS) showed as **asterisks** and **green arrows**. **(B)** Patients with paced fQRS (Frag[+]) had a significantly higher risk for cardiac death and/or heart failure (HF) than did those patients without paced fQRS (Frag[−]). **(C)** Patients with paced fQRS had a significantly higher risk for ventricular arrhythmias (VAs) than did those patients without paced fQRS. CRT = cardiac resynchronization therapy.

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https://doi.org/10.1016/j.jacep.2022.01.004

This work was supported by the National Cerebral and Cardiovascular Center (grant 25-4-7 [to K.K.]). Dr Noda was partially supported by Japan Society for the Promotion of Science Kakenhi (grant JP085700004). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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