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CME

Radiofrequency Ablation of Premature Ventricular Ectopy Improves the Efficacy of Cardiac Resynchronization Therapy in Nonresponders

Dhanunjaya Lakkireddy, MD,* Luigi Di Biase, MD, PhD,†‡§ Kay Ryschon, MS,* Mazda Biria, MD,* Vijay Swarup, MD,‖ Yeruva Madhu Reddy, MD,* Atul Verma, MD,¶ Sudharani Bommana, MPhil,* David Burkhardt, MD,† Raghuveer Dendi, MD,* Antonio Dello Russo, MD, PhD,# Michela Casella, MD, PhD,# Corrado Carbucicchio, MD,# Claudio Tondo, MD, PhD,# Buddhadeb Dawn, MD,* Andrea Natale, MD†‡

Kansas City, Kansas; Austin, Texas; Phoenix, Arizona; Southlake, Ontario, Canada; and Foggia and Milan, Italy

JACC JOURNAL CME

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CME Objective for This Article: At the conclusion of this activity, the learner should be able to determine whether suppressing PVCs using radiofrequency ablation improves effectiveness of the CRT in nonresponders.

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From the *Division of Cardiovascular Diseases, Cardiovascular Research Institute, University of Kansas Hospital and Medical Center, Kansas City, Kansas; †Texas Cardiac Arrhythmia Institute, Austin, Texas; ‡Department of Biomedical Engineering, University of Texas, Austin, Texas; §Department of Cardiology, University of Foggia, Foggia, Italy; ‖Arizona Heart Rhythm Center, Phoenix, Arizona; ¶Southlake Regional Hospital, Southlake, Ontario, Canada; and the #Cardiac Arrhythmia Research Centre, Centro Cardiologico Monzino, Istituto Di Ricovero e Cura a Carattere Scientifico, Milan, Italy. Dr. Lakkireddy has received modest speaker/consulting honoraria from St. Jude Medical, Boehringer Ingelheim, and Jansen. Dr. Di Biase is a consultant for Hansen Medical and Biosense Webster. Dr. Verma has received research grants from Medtronic and St. Jude Medical. Dr. Burkhardt a consultant for Stereotaxis and Biosense Webster. Dr. Tondo is a member of the advisory boards of Biosense Webster and Biotronik; and has received lecture fees from St. Jude Medical. Dr. Natale has received speaker honoraria from Boston Scientific, Biosense Webster, St. Jude Medical, Biotronik, and Life Watch. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Lakkireddy and Di Biase contributed equally to this work and both should be considered as co-first authors.

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Radiofrequency Ablation of Premature Ventricular Ectopy Improves the Efficacy of Cardiac Resynchronization Therapy in Nonresponders

Objectives This study sought to examine whether suppressing premature ventricular contractions (PVC) using radiofrequency ablation improves effectiveness of the cardiac resynchronization therapy (CRT) in nonresponders.

Background CRT is an effective strategy for drug refractory congestive heart failure. However, one-third of patients with CRT do not respond clinically, and the causes for nonresponse are poorly understood. Whether frequent PVC contribute to CRT nonresponse remains unknown.

Methods In this multicenter study, CRT nonresponders with >10,000 PVC in 24 h who underwent PVC ablation were enrolled from a prospective database.

Results Sixty-five subjects (age 66.6 ± 12.4 years, 78% men, QRS duration of 155 ± 18 ms) had radiofrequency ablation of PVC from 76 foci. Acute and long-term success rates of ablation were 91% and 88% in 12 ± 4 months of follow-up. There was significant improvement in left ventricular (LV) ejection fraction (26.2 ± 5.5% to 32.7 ± 6.7 %, $p < 0.001$), LV end-systolic diameter (5.93 ± 0.55 cm to 5.62 ± 0.32 cm, $p < 0.001$), LV end-diastolic diameter (6.83 ± 0.83 cm to 6.51 ± 0.91 cm, $p < 0.001$), LV end-systolic volume (178 ± 72 to 145 ± 23 ml, $p < 0.001$), LV end-diastolic volume (242 ± 85 ml to 212 ± 63 ml, $p < 0.001$), and median New York Heart Association functional class (3.0 to 2.0, $p < 0.001$). Modeling of pre-ablation PVC burden revealed an improvement in ejection fraction when the pre-ablation PVC burden was >22% in 24 h.

Conclusions Frequent PVC is an uncommon yet significant cause of CRT nonresponse. Radiofrequency ablation of PVC foci improves LV function and New York Heart Association class and promotes reverse remodeling in CRT nonresponders. PVC ablation may be used to enhance CRT efficacy in nonresponders with significant PVC burden. (J Am Coll Cardiol 2012;60:1531–9) © 2012 by the American College of Cardiology Foundation

Cardiac resynchronization therapy (CRT) is an effective and established treatment for patients with drug-refractory congestive heart failure and significant electromechanical delay. Several studies have clearly established a beneficial role of CRT in improving the functional status and hemodynamic and echocardiographic parameters in heart failure patients (1–6). Improvement in functional status has been used as the direct marker of response to CRT in previous clinical studies (7). Change in ejection fraction, end-systolic volume, degree of mitral regurgitation, and cardiac output have been used as surrogate markers for response to CRT using echocardiographic data (8–10). However, it is also known that nearly 30% (range 18% to 52%) (11,12) of patients who meet the criteria for implantation will not respond to CRT. Considering the complexity and the economic impact of CRT, it is important to maximize the number of responders to this approach. In this regard, studies have shown the importance of effective biventricular capture in CRT responders (13), and it is predictable that subjects with high premature ventricular contraction (PVC) burden will have decreased effective biventricular pacing. The presence of fusion or pseudofusion beats due to high PVC burden can also decrease the response to CRT (14). This could hinder the ventricular reverse remodeling accomplished by restoration of mechanical and electrical resynchronization through CRT (15).

A bidirectional nature of cause-and-effect relationship between PVC and cardiomyopathy has been proposed in the past (16). Studies have shown that gradual deterioration of ejection fraction can be seen in subjects with normal systolic function who have frequent PVC (17). High PVC burden is a significant but less known cause of heart failure (18) and carries a poor prognosis (19). Improvement in systolic function after PVC suppression has been reported in subjects with high PVC burden in the past (20–22). Earlier studies have shown that patients who have a positive response to CRT often experience a reduction in ventricular arrhythmia burden (23–25). The effect of PVC ablation in subjects who are considered nonresponders to CRT has been reported in case reports (26), but it has not been investigated in a large study.

Methods

This was a prospective, multicenter, nonrandomized observational study that assessed the effect of PVC ablation in consecutive subjects considered nonresponders to CRT with high PVC burden. All subjects who underwent CRT implantation between January 2007 and June 2010 were screened for the study. Any patient who had received or upgraded to a clinically indicated biventricular pacemaker or defibrillator was considered for this study. Patients were eligible if they had <5% improvement in the left ventricular ejection fraction (LVEF) and or LV end-systolic volume of <10% with no associated improvement in clinical status 1 year after CRT implantation (27). These patients were considered nonresponders. All subjects had echocardiography within 4 weeks prior to PVC ablation and 6 months after ablation to assess LV function and LV dimensions.

Frequent PVC were considered a potential cause of non-CRT response and were further screened. Those patients who had >10,000 PVC in a 24-h period documented by a Holter monitoring were considered to have a significant PVC burden and were thus enrolled in the study (28). Patients who had sustained ventricular tachycardia requiring antitachycardia pacing or shock therapy were excluded. Similarly, patients with atrial fibrillation burden of more than 1% were also excluded from the study. Beta-blocker therapy was maximized as tolerated by the patient once patients with significant clinical burden of frequent PVC were identified. Antiarrhythmic drugs were used at the discretion of the treating physician.

PVC ablation. All patients who met the inclusion criteria were offered the PVC ablation. All subjects were informed of the benefits and risks of the procedure and consented under direction of the respective institutional review boards and human subject committees.

Eligible patients underwent electrophysiology study and radiofrequency ablation (RFA) of the PVC. If >1 PVC focus was identified, then an attempt was made to ablate all morphologies. An attempt was made to assess the site of origin based on the surface 12-lead electrocardiogram or 12-lead Holter prior to the ablation. The right ventricle was mapped via the standard femoral approach and the LV was mapped via a transseptal or retrograde aortic approach. Epicardial access was obtained as deemed necessary by the operator. The patient was anticoagulated with unfractionated heparin for activated clotting time of 300 to 350 s for all left-sided procedures. Remote magnetic-guided navigation (Stereotaxis, St. Louis, Missouri) was used for mapping and ablation based on operator choice. In addition to the standard diagnostic catheters, 3-dimensional electroanatomic mapping (Carto, Biosense Webster Inc., Diamond Bar, California; or NavX/Array, St. Jude Medical Inc., St. Paul, Minnesota) was used in all procedures (Fig. 1). Intracardiac echocardiography (Acunav, Siemens, Mountain View, California) was used in all patients to guide transseptal and epicardial accesses and also to monitor catheter location and pericardial effusion. RFA was performed through an open irrigated ablation catheter (Thermocool Celsius or Navistar, Biosense Webster Inc.). Anatomic and activation mapping were performed simultaneously. The earliest activation point that matched pace mapping was targeted for ablation. Pace mapping was performed in all cases to confirm the site of origin of the PVC. Voltages were defined as follows: <0.5 mV as scar; 0.5 to 1.5 mV as the border zone. The vast majority of patients underwent the procedure under conscious sedation with only a few requiring general anesthesia. Intravenous isoproterenol (up to 10 μg/min for 10 min), caffeine (250 mg over 20 min), calcium chloride (1 g over 10 min), and phenylephrine (≤5 μg/kg for 10 min) were also infused as

Abbreviations and Acronyms

BiV = biventricular
CRT = cardiac resynchronization therapy
EF = ejection fraction
LV = left ventricle/ventricular
LVEF = left ventricular ejection fraction
NYHA = New York Heart Association
PVC = premature ventricular contraction(s)
RFA = radiofrequency ablation

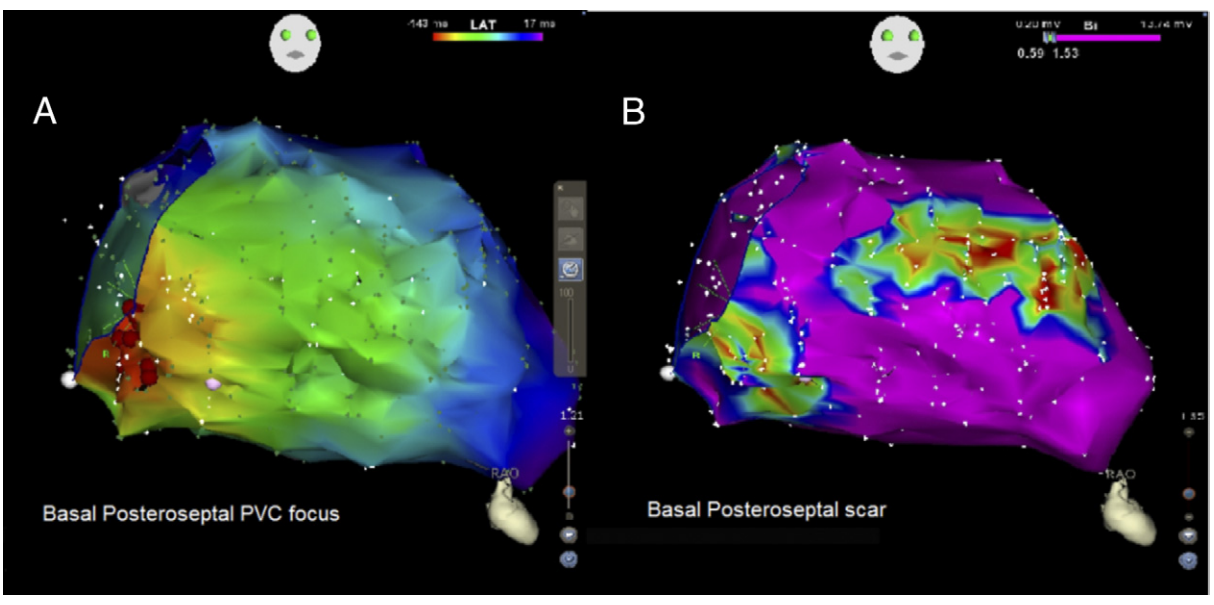

Figure 1 Voltage and Activation Map in a Patient Undergoing PVC Ablation

(A) The earliest site of activation along the postero-basal septum on Carto linear activation time map (Biosense Webster Inc., Diamond Bar, California) is shown. **(B)** Voltage map showing scar along the postero-basal septal distribution of the left ventricle corresponding to the premature ventricular contraction (PVC) focus.

JACC Vol. 60, No. 16, 2012
October 16, 2012:1531–9

deemed necessary for induction of ectopy during the procedure if there was paucity of PVC impeding activation mapping. If PVC remained infrequent, pace-mapping was performed at a pacing cycle length that matched the coupling interval of the spontaneous ventricular ectopy (29). Complete abatement of clinical PVC after RFA was targeted whenever possible. Patients were monitored for a minimum of 30 min after the last radiofrequency application to ensure complete abatement of the ventricular ectopy. If >1 PVC focus was seen, then the most frequent one was targeted first followed by the infrequent ones. All patients were monitored overnight on the day of the procedure and were discharged the following day.

Assessment of LV function and dimensions. A baseline echocardiogram was performed within a 4-week window before RFA. A follow-up echocardiogram was performed to assess LV function and dimensions at 6 months after the procedure. Echocardiograms were assessed by 2 independent echocardiographers who were blinded to the study and outcome of the ablation procedure. LVEF was calculated by Simpson formula when 2 consecutive biventricular paced beats were present, using the second paced beat for analysis of the ejection fraction to avoid post-extrasystolic potentiation of LV function.

Assessment of PVC burden. To assess clinical response, all patients were monitored using 24-h Holter telemetry at 48 h, 3 months, and 6 months after ablation. The PVC burden noted on the CRT device was also used to confirm the results from Holter telemetry. If the PVC burden was <1,000 per 24-h period, the procedure was considered to be successful.

Statistical analysis. SPSS Statistical Package (version 16.0, SPSS Inc., Chicago, Illinois) was used for statistical analysis. Continuous data were summarized by mean ± SD, categorical by percentages, and ordinal by median and interquartile range.

Post-PVC ablation continuous clinical and echocardiographic data was compared to pre-ablation values using the paired *t* test, and ordinal data was compared using the Wilcoxon signed rank test. Pre-ablation PVC burden groups (i.e., ≤22 and >22) were compared using Student independent *t* test or the Mann-Whitney *U* test as appropriate for continuous or ordinal data. Repeated measure analysis was performed using the general linear model procedure to test significant analysis of variance with post hoc Bonferroni testing was used for multiple comparisons of echo parameters and Kruskal-Wallis was used for New York Heart Association (NYHA) functional class. A linear model was used to identify the point estimate for pre-ablation biventricular pacing percentage corresponding to zero EF improvement. Results are shown graphically along with significant correlation coefficients. A p value <0.05 was considered significant.

Results

Baseline characteristics. A total of 2,034 patients who had CRT were screened. Of these patients, 509 (25%) were considered nonresponders. Among the nonresponders, 13% (65 of 509) met the criteria of significant PVC burden (age: 67 ± 12 years, men: women: 3.6:1, QRS duration of 155 ± 18 ms). Hypertension was present in 65% of these patients and diabetes in 52%. Ischemic cardiomyopathy was present in 35%. The most common QRS morphology was left bundle branch block, which was present in 59%. Other clinical and demographic characteristics are outlined in Table 1.

The average time from CRT implant to PVC ablation was 14.8 ± 6.1 months.

Procedural characteristics. Seventy-six foci were ablated in 65 patients. The vast majority had a single focus (86%) with the remaining patients having ≥2 foci. Carto was used

Table 1 Baseline Characteristics

Age, yrs	66.6 ± 12.4
Sex, M/F	3.6/1.0
CRT device type	
CRTD	61 (93.8%)
CRTP	4 (6.2)
Median NYHA functional class	3.0
Cardiomyopathy type	
DCM	42 (64.6)
ICM	23 (35.4)
QRS width, ms	155.2 ± 17.9
Underlying QRS morphology	
IVCD	7 (10.8)
LBBB	38 (58.5)
Paced	11 (16.9)
RBBB	9 (13.8)
Comorbidities	
Diabetes	34 (52.3)
HTN	42 (64.6)
Hyperlipidemia	38 (58.5)
CAD	29 (44.6)
Chronic renal insufficiency (Cr >1.5)	11 (16.9)
Ventricular fibrillation	21 (32.3)
Medications	
Beta blocker	65 (100)
ACE inhibitor	62 (95.4)
Antiarrhythmic drugs	9 (13.8)
Echo parameters	
LVEF, %	26.2 ± 5.5
LVESD, cm	5.93 ± 0.55
LVEDD, cm	6.83 ± 0.93
LVESV, ml	178 ± 72
LVEDV, ml	242 ± 85
Percentage of pre-ablation PVC burden	
10%–20%	27 (41.5)
20.1%–30%	20 (30.8)
30.1%–40%	9 (13.8)
>40.1%	9 (13.8)

Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme; CAD = coronary artery disease; CRT = cardiac resynchronization therapy; CRTD = cardiac resynchronization therapy-defibrillator; CRTP = cardiac resynchronization therapy-pacemaker; DCM = dilated cardiomyopathy; HTN = hypertension; ICM = ischemic cardiomyopathy; IVCD = intraventricular conduction defect; LBBB = left bundle branch block; LVEDD = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVESV = left ventricular end-systolic volume; NYHA = New York Heart Association; PVC = premature ventricular contraction; RBBB = right bundle branch block.

Table 2 Procedural Characteristics

Intraprocedural Variable	
Number of clinical PVC	
1	56 (86.2)
2	7 (10.8)
3	2 (3.1)
Type of 3D electroanatomic mapping	
Carto	51 (78.5)
NavX	14 (21.5)
Remote magnetic-guided navigation	18 (27.7)
Intracardiac echocardiography	65 (100)
Mean procedure time, min	157.2 ± 44.8
Procedural complications	2 (3.0)
Tamponade	1 (1.5)
TIA	1 (1.5)
Acute successful PVC ablation	
Yes	69 (90.8)
No	7 (9.2)

Values are n (%) or mean ± SD. Carto is a product of Biosense Webster Inc. (Diamond Bar, California), and NavX is a product of St. Jude Medical Inc. (St. Paul, Minnesota).
3D = 3-dimensional; PVC = premature ventricular contraction; TIA = transient ischemic attack.

more frequently than NavX was (78.5% vs. 21.5%). Remote magnetic navigation was used in 28% of patients. The mean procedural duration was 157 ± 45 min. Sixty-nine of the 76 (90.8%) foci was successfully ablated (Table 2). LV was the most common source of the PVC (75%) with the right ventricle being the source of ectopy in 25%. Epicardial focus was ablated in 4 (6%) patients. Submitral annulus (29%) and right ventricular outflow tract (16%) were the most common sites of origin. The distribution of other sites of origin is outlined in Table 3.

Follow-up and procedural outcomes. Acute success was seen in 91% of patients with only 2 patients experiencing procedure-related complications (transient ischemic attack in 1 and pericardial tamponade in the other). During a mean follow-up period of 12 ± 4 months, the procedural success remained high at 88% (PVC burden <1,000 per 24 h). In 3% (n = 2) who had acute success but late recurrence, there was recurrence of PVC and 1 underwent repeat ablation while the other was treated with antiarrhythmic drugs. There were no deaths or any other major comorbid events during the follow-up period.

Effect of ablation on echo parameters and NYHA class. Follow-up echocardiography 6 months after ablation revealed CRT response with improvements in mean LVEF (26.2 ± 5.5% to 32.7 ± 6.7%, $p < 0.001$), LV end-systolic diameter (5.83 ± 0.55 cm to 5.62 ± 0.32 cm, $p < 0.001$), LV end-diastolic diameter (6.83 ± 0.83 cm to 6.51 ± 0.91 cm, $p < 0.001$), LV end-systolic volume (178 ± 72 ml to 145 ± 23 ml, $p < 0.001$), LV end-diastolic volume (242 ± 85 ml to 212 ± 63 ml, $p < 0.001$), and median NYHA class (3.0 to 2.0, $p < 0.001$) (Table 4).

Correlation between severity of PVC burden and CRT response after PVC ablation. The pre-ablation PVC burden was stratified into 3 categories based on PVC frequency as a percentage of all beats: 10% to 20%, 20.1% to 30%, >30%. The resulting average improvement in echo parameters is shown for each category in Table 5. The greatest change was seen in those patients who had the highest percentage of pre-ablation PVC burden (>30%) (Table 5). Modeling of the percentage of pre-ablation PVC burden on the improvement in EF found that EF improved (>0%) when the percentage of pre-ablation PVC burden was greater than 14.3% and for a clinically significant improvement in EF the pre-ablation PVC burden was 22% (Fig. 2). The difference in improvement in echo parameters and NYHA class between patients with a pre-ablation PVC burden of ≤22 vs. >22% is shown in Table 6.

Effect of PVC ablation on biventricular pacing. The mean biventricular pacing frequency (expressed as a percentage) before PVC ablation was 76 ± 12% (range 37% to 90%). After ablation, the mean biventricular (BiV) pacing frequency improved significantly to 98 ± 2% ($p < 0.001$, range 96% to 100%). Because the percentage of BiV pacing frequency was inversely correlated to the PVC burden, there was an inverse correlation between the pre-ablation BiV pacing frequency and the degree of improvement in LVEF (Fig. 3).

Effects of turning off CRT following successful PVC ablation. A clinical decision was made in a subset of 25 patients to turn off BiV pacing 6 months after successful

Table 3 Site of Origin of PVCs

Left ventricle	
LV—submitral annulus	22 (28.94)
LV—mid posterior	4 (5.26)
LV— apex	4 (5.26)
LV—distal posterolateral	4 (5.26)
LV—distal posterior	3 (3.95)
LV—outflow tract	2 (2.63)
LV—posterior papillary muscle	2 (2.63)
LV—left aortic cusp	2 (2.63)
LV—distal left posterior fascicle	2 (2.63)
LV—aortomitral continuity	2 (2.63)
LV—right aortic cusp	1 (1.32)
Epicardial LV—basal posterolateral (coronary sinus access)	1 (1.32)
Epicardial LV—mid anterior	1 (1.32)
Epicardial LV—subapical	1 (1.32)
Epicardial LV—apex	1 (1.32)
LV—mid anterior	2 (2.63)
LV—distal posterior septal	1 (1.32)
LV—distal left anterior fascicle	1 (1.32)
LV—distal anteroseptal	1 (1.32)
Right ventricle	
RV—outflow tract	12 (15.78)
RV—posterior sub-tricuspid	2 (2.63)
RV—parahisian	2 (2.63)
RV—distal septum	1 (1.32)
RV—free wall	1 (1.32)
RV—apex	1 (1.32)
Total	76 (100.0)

RV = right ventricle; other abbreviations as in Tables 1 and 2.

Table 4 Change in Various Echo Parameters Before and After PVC Ablation

Change in Echo Parameters	Pre-Ablation	Post-Ablation	Mean Improvement	p Value
Δ EF	26.2 ± 5.5	32.7 ± 6.7	6.42 ± 5.26	<0.001
Δ LVEDD	6.83 ± 0.83	6.51 ± 0.91	−0.32 ± 0.26	<0.001
Δ LVESD	5.83 ± 0.55	5.62 ± 0.32	−0.31 ± 0.23	<0.001
Δ LVESV	178 ± 72	145 ± 23	−33.17 ± 22.94	<0.001
Δ LVEDV	242 ± 85	212 ± 63	−30.65 ± 21.63	<0.001

Values are mean ± SD.
Abbreviations as in Tables 1 and 2.

ablation of the PVC to assess the true impact of PVC ablation on LV function. The CRT was off for 6 months and patients' clinical status along with echo parameters were reassessed. The echocardiography parameters and NYHA class of these patients (Table 7) show that after the CRT was turned off, the EF and LV systolic and diastolic diameters and volumes returned to the pre-ablation values in these patients. These data indicate the importance of CRT in LV remodeling and suggest that the therapeutic benefits of PVC ablation were largely related to improvement in BiV pacing in these patients.

Differences between responders and nonresponders after PVC ablation. About 34% (n = 22) of patients who had the PVC ablation did not respond (<5% improvement in LVEF from post-CRT to post-ablation). Table 8 describes these differences between the post-PVC ablation responders and nonresponders. Responders had significantly higher PVC burden (28.7 ± 12.2 vs. 16.2 ± 5.0, $p < 0.001$), lower pre-ablation BiV pacing (71.3 ± 12.2 vs. 83.8 ± 5.0, $p < 0.001$), and a significantly higher post-ablation LVEF (35.1 ± 5.5 vs. 27.9 ± 6.4, $p < 0.001$).

Discussion

Salient findings. Our results show that: 1) high PVC burden is a potential cause of CRT nonresponse; 2) RFA of the PVC focus improves LVEF, LV dimensions, and NYHA functional class in CRT nonresponders; 3) the gains in LV function and NYHA class are directly proportional to the pre-ablation PVC burden; 4) a pre-ablation PVC burden greater than 22% is associated with the greatest improvement in CRT response as measured by LVEF, LV dimensions, and NYHA class; and 5) the benefits of PVC ablation are largely related to an increase in effective BiV pacing. The current results constitute the first evidence that improved CRT response can be achieved through RFA of PVC in nonresponders with a high PVC burden.

Frequent PVC and LV dysfunction. The precise prevalence of high PVC burden in the general population and in those with LV dysfunction remains unknown. In the current study, 13% of subjects with known cardiomyopathy and wide QRS who were nonresponders to CRT had a significant PVC burden (> 10,000 PVCs in 24 h). Frequent idiopathic PVC may be benign from a sudden cardiac death standpoint, but may result in a reversible form of LV dysfunction (30,31). PVC can not only cause LV dysfunction in patients with no underlying structural heart disease, but they can also worsen LV function in those with known cardiomyopathy and underlying scar (32,33). However, the pathophysiology behind PVC-mediated cardiomyopathy is unclear. Possible mechanisms include dysynchronous ventricular activation, impaired calcium handling, or a decrease in calcium transient (34,35). Even in patients with underlying structural heart disease and cardiomyopathy with frequent PVC, the LV dysfunction may be partially reversible if the PVC can be abated. Indeed, several studies have shown that abatement of frequent PVC through RFA may result in significant improvement and sometimes normal-

Table 5 Change in Echo Parameters After Ablation Stratified by Percentage of PVC Burden

Δ in Echo Parameters	Pre-Ablation PVC Burden			1-Way ANOVA p Value	Bonferroni Post-Hoc Testing
	10% to 20%, n = 27	20.1% to 30%, n = 20	>30%, n = 18		
Δ EF, pre-ablation	3.11 ± 3.54	5.60 ± 2.64	12.28 ± 4.75	<0.001	3 differs from 1, 2 (<0.001) 1 differs from 2 (<0.05)
Δ LVEDD, cm	−0.20 ± 0.17	−0.23 ± 0.16	−0.62 ± 0.20	<0.001	3 differs from 1, 2 (<0.001) 1 does not differ from 2 (NS)
Δ LVESD, cm	−0.18 ± 0.18	−0.28 ± 0.18	−0.55 ± 0.17	<0.001	3 differs from 1, 2 (<0.001) 1 does not differ from 2 (NS)
Δ LVEDV, ml	−11.2 ± 12.9	−35.5 ± 13.7	−54.5 ± 8.1	<0.001	All differ from each other (<0.001)
Δ LVESV, ml	−17.6 ± 15.6	−27.1 ± 9.8	−63.3 ± 10.8	<0.001	3 differs from 1, 2 (<0.001) 1 differs from 2 (<0.05)
NYHA class	−1.000 (−1.00 to 0.00)	0.000 (−1.00 to 0.00)	−1.000 (−1.00 to −0.75)	0.062*	

Values are mean ± SD or median (interquartile range). *Kruskal-Wallis test was used for statistical comparisons.
NS = not significant; NYHA = New York Heart Association; other abbreviations as in Tables 1 and 2.

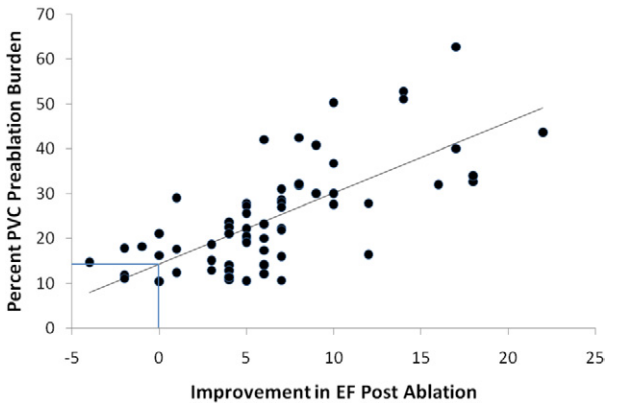

Figure 2 **Correlation Between PVC Burden and EF Change Following Ablation**

Percentage of pre-ablation premature ventricular contraction (PVC) burden and correlation with change in post-ablation ejection fraction (EF). The figure shows a Pearson correlation coefficient of 0.699, which is statistically significant at $p < 0.001$ (2-tailed). BiV = biventricular.

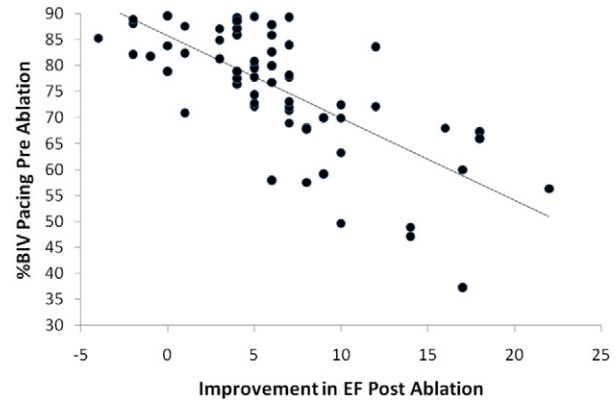

Figure 3 **Correlation Between Pre-Ablation BIV Pacing % and Post-Ablation Improvement in EF**

The figure shows a Pearson's correlation coefficient of 0.699 which is statistically significant at $p < 0.001$ (2-tailed). BIV = biventricular pacinig; EF = ejection fraction.

ization of LV function and LV dimensions in patients with and without baseline LV dysfunction (30,32,33).

CRT nonresponse and PVC ablation. It has now become apparent that 25% to 30% of patients with drug refractory LV dysfunction and heart failure will not respond to CRT. However, the causes for this lack of response remain unclear. Our study is the first to describe the correlation between high PVC burden and CRT nonresponse. It has been shown that patients with a higher percentage of BiV pacing derive the most benefit from CRT with resultant gains in LVEF and functional class (36). As is shown by our results, frequent PVC can reduce the percentage of BiV pacing, thereby hindering the reverse remodeling and increase substrate changes that promote worsening LV dysfunction. When revascularization, pharmacotherapy, and CRT optimization options have been exhausted, identification and abatement of frequent PVC may offer an excellent strategy to improve LV function and clinical response in CRT nonresponders.

Table 6 **Improvements in Echo Parameters and NYHA Class Post-Ablation With Percentage of Pre-Ablation PVC Burden Stratified to <22% and >22%**

Change in Echo Parameters	Pre-Ablation PVC Ablation		Independent *t* Test p Value
	≤22.0%, n = 33	>22.0%, n = 32	
Δ EF	4.79 ± 7.25	12.66 ± 7.54	<0.001
Δ LVEDD	−0.18 ± 0.18	−0.47 ± 0.24	<0.001
Δ LVESD	−0.17 ± 0.19	−0.46 ± 0.18	<0.001
Δ LVESV	−18.7 ± 15.4	−48.1 ± 19.8	<0.001
Δ LVEDV	−16.0 ± 17.8	−45.8 ± 13.2	<0.001
Δ NYHA class	−1.00 (−1.00, 0.00)	−1.0 (−1.00, 0.00)	0.525*

Values are mean ± SD and median (interquartile range). *Mann-Whitney *U* test was used for statistical comparisons.

Abbreviations as in Tables 1, 2, and 5.

This concept is further supported by the findings in the subset of 25 patients who had the CRT turned off 1 year after successful PVC ablation. As shown in Table 7, the improvement in NYHA class and reverse remodeling evidenced by echocardiographic parameters after PVC ablation in these patients were lost 6 months after the CRT was turned off. These observations underscore the importance of CRT as the mechanistic basis of improvement after PVC ablation. In conjunction with the BiV pacing frequency data, these results also suggest that PVC ablation renders these patients responders to BiV pacing.

Factors determining the success of PVC ablation in improving LV function. Abatement of frequent PVC and the incremental benefit of increased BiV pacing and myocardial reverse remodeling seem to be 1 of the reasons for the overall improvement in EF in patients after PVC ablation. Our data show that the degree of PVC burden and the pre-ablation BiV pacing percentage are important factors that determine whether PVC ablation will result in significant improvement in LV function. In prior studies (31–33), this number has ranged from 5% to 24%. In a previous study (31), the presence of LV myocardial scar was found to be a significant predictor for the improvement of LV function after a PVC ablation. Our results indicate that pre-ablation PVC burden greater than 22% is associated with a statistically significant improvement in LV function following RFA. Incidentally, all of our patients had structural heart disease in the form of ischemic or idiopathic cardiomyopathy with manifest scar on the voltage maps.

Clinical trials on CRT implantation have shown an absolute increase of 5% in EF in implanted subjects as a measure of CRT response (37). We elected to use EF (instead of dysynchrony indices or volume measurements) to measure response to CRT, because it is the most commonly measured cardiac function by different modalities and its

JACC Vol. 60, No. 16, 2012
October 16, 2012:1531–9

Table 7 Serial Echo Parameters and NYHA Class Before and 6 Months After Successful PVC Ablation, and 6 Months After BiV Pacing Was Turned Off

Echo Parameters	Time Point 1 Pre-Ablation % (n = 25)	Time Point 2 6 Months Post-Ablation CRT-ON, (n = 25)	Time Point 3 1-Year Post-Ablation CRT-OFF (n = 25)	p Value From Paired Comparison		
				1 vs. 2	1 vs. 3	2 vs. 3
EF	25.8 ± 5	34.8 ± 4	24.9 ± 6	<0.001	0.707	<0.001
LVEDD, cm	6.83 ± 0.83	5.23 ± 0.54	7.28 ± 1	0.013	0.098	<0.001
LVESD, cm	5.48 ± 0.75	4.78 ± 0.5	6.10 ± 0.95	0.006	0.072	<0.001
LVESV, ml	169 ± 62	152 ± 56	187 ± 58	0.373	0.310	0.013
LVEDV, ml	233 ± 55	217 ± 42	241 ± 85	0.259	0.241	0.006
Median NYHA class	3	2	3	<0.001	0.948	<0.001

Values are mean ± SD. Only a subset of patients who improved their EF (delta >0%) had BiV pacing turned off.
BiV = biventricular; other abbreviations as in Tables 1, 2, 3, and 5.

correlation to mortality is well known from previous studies (38,39). However, our study also showed a significant decrease in cardiac dimensions following ablation.

Table 8 Shows the Differences Between Post-PVC Ablation Responders Versus Nonresponders

Clinical Variables	Responders (n = 43)	Nonresponders (n = 22)	p Value
Age, yrs	66.7 ± 12.1	66.5 ± 13.1	0.969
Sex, M/F	34 (79.1)/9 (20.9)	17 (77.3)/ 5 (22.7)	0.868
Cardiomyopathy			0.328
DCM	26 (60.5)	16 (72.7)	
ICM	17 (39.5)	6 (27.3)	
NYHA class pre-ablation			0.345
2	6 (14.0)	1 (4.5)	
3	33 (76.7)	17 (77.3)	
4	4 (9.3)	4 (18.2)	
Previous device			
ICD	11 (25.6)	6 (27.3)	0.949
PPM	5 (11.6)	2 (9.1)	
None	27 (62.8)	14 (63.6)	
Device type			0.700
CRTD	40 (93.0)	21 (95.5)	
CRTP	3 (7.0)	1 (4.5)	
Baseline QRS width	153.2 ± 18.1	159.2 ± 17.1	0.197
History of diabetes	21 (48.8)	13 (59.1)	0.434
History of HTN	26 (60.5)	16 (72.7)	0.328
History of hyperlipidemia	21 (48.6)	17 (77.3)	0.028
History of CAD	22 (51.2)	7 (31.8)	0.138
History of CRI	7 (16.3)	4 (18.2)	0.846
Successful ablation	45/49 (91.8)	24/27 (88.9)	0.878
Δ LVEDD	−0.44 ± 0.22	−0.11 ± 0.16	<0.001
Δ LVESD	−0.40 ± 0.22	−0.13 ± 0.15	<0.001
Δ LVESV	−44.1 ± 19.2	−11.9 ± 12.0	<0.001
Δ LVEDV	−41.0 ± 16.8	−10.3 ± 14.5	<0.001
Post-ablation EF	35.1 ± 5.5	27.9 ± 6.4	<0.001
PVC burden before	28.7 ± 12.2	16.2 ± 5.0	<0.001
BiV pacing before	71.3 ± 12.2	83.8 ± 5.0	<0.001
BiV pacing after	99.7 ± 0.8	99.8 ± 0.5	0.691
Δ BiV pacing post-PVC ablation	28.4 ± 12.1	16.0 ± 4.9	<0.001

Values are mean ± SD or n (%).
CRI = Chronic renal insufficiency; CRTD = cardiac resynchronization therapy-defibrillator; CRTP = cardiac resynchronization therapy-pacemaker; PPM = permanent pacemaker; other abbreviations as in Tables 1, 5, and 7.

Study limitations. The following are the limitations of the current study. 1) The patients did not have an echo immediately after the ablation as it may take several days for PVC abatement to translate into meaningful effect on reverse remodeling of the LV. 2) The long-term impact of PVC ablation on CRT response and survival could not be determined in this study.

The data suggest that most of the benefit from PVC ablation is probably related to the improved biventricular pacing. However, in the absence of a control group with continued high PVC burden and ineffective CRT, we cannot completely exclude whether tachycardia-mediated cardiomyopathy plays a role in CRT nonresponse in addition to the effective BiV pacing. In this respect, the real long-term time course of response to CRT with regard to PVC burden is largely unknown. However, it is unlikely that nonresponders to CRT would experience disappearance of PVC over a longer follow-up as the average time from CRT implant to PVC ablation was 14.8 ± 6.1 months. Indeed, we believe that patients with continued high PVC burden even after 1 year following CRT implant would derive significant clinical benefit from PVC abatement through ablation. Incidentally, 34% of patients who had successful PVC ablation resulting in more than 99% BiVpacing continued to be nonresponders. However, this group reflects the patients with lower PVC burden.

Conclusions

Frequent PVCs are a less common but important and treatable cause of nonresponse to CRT. Successful RFA of PVC foci improves LV function and NYHA class and promotes reverse remodeling in CRT nonresponders. Thus, PVC ablation may be used to enhance CRT efficacy in nonresponders with significant PVC burden.

Reprint requests and correspondence: Dr. Dhanunjaya Lakkireddy, Center for Excellence in Atrial Fibrillation/Complex Arrhythmia Management, Bloch Heart Rhythm Center at University of Kansas Hospital, 3901 Rainbow Boulevard, MS 4023, Kansas City, Kansas 66160-7200. E-mail: dlakkireddy@mac.md.

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Key Words: cardiac resynchronization therapy ■ premature ventricular contraction ■ radiofrequency ablation.