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Neurohormonal, Structural, and Functional Recovery Pattern After Premature Ventricular Complex Ablation Is Independent of Structural Heart Disease Status in Patients With Depressed Left Ventricular Ejection Fraction

A Prospective Multicenter Study

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Objectives This study aimed to assess the benefit after ablation of premature ventricular complexes (PVC) in patients with frequent PVC and left ventricular (LV) dysfunction, regardless of previous structural heart disease (SHD) diagnosis, PVC morphology, or estimated site of origin.

Background Ablation of PVC in patients with LV dysfunction is usually restricted to patients with suspected PVC-induced cardiomyopathy.

Methods Consecutive patients with frequent PVC and LV dysfunction accepted for ablation at 4 centers were prospectively included. Of the 80 patients included, 27 (34%) had a diagnosis of SHD.

Results Successful sustained ablation (SSA) was achieved in 53 (66%) patients, and LVEF improved in these patients from 33.7 ± 8% to 43.8 ± 9.4% and 45.8 ± 10.9% at 6 and 12 months, respectively ($p < 0.05$), without differences related to previous diagnosis of SHD ($p = 0.69$). BNP decreased from 109 [64 to 242] pg/ml to 60 [25 to 170] pg/ml, 50 [14 to 130] pg/ml, and 60 [19 to 81] pg/ml at 1, 6, and 12 months ($p < 0.05$). Patients in NYHA class I increased from 12 (23%) to 42 (79%) at 12 months ($p < 0.05$). A 13% baseline PVC burden had 100% sensitivity and 85% specificity to predict an absolute increase ≥5% in LVEF after SSA. Although 20 patients with >13% PVC and SSA had class I indication for cardioverter defibrillator implantation, these indications were absent at 6 months post-ablation.

Conclusions Independently of the presence of SHD, the SSA of frequent PVC in patients with depressed LVEF induced a progressive clinical and functional improvement. Improvement in heart failure parameters was related to baseline PVC burden and persistence of ablation success. (J Am Coll Cardiol 2013;62:1195–202) © 2013 by the American College of Cardiology Foundation

There is increasing interest in identifying patients with frequent premature ventricular complexes (PVC) and left ventricular (LV) dysfunction who may benefit from catheter ablation. Small, single-center, observational studies have reported that radiofrequency catheter ablation (RFCA) of PVC can improve left ventricular ejection fraction (LVEF)

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JACC Vol. 62, No. 13, 2013
September 24, 2013:1195–202

Abbreviations and Acronyms

BNP = brain natriuretic peptide
ce-CMR = contrast-enhanced cardiac magnetic resonance
ECG = electrocardiogram
ICD = implantable cardioverter-defibrillator
IHD = ischemic heart disease
LVEF = left ventricular ejection fraction
NT proBNP = N-terminal pro brain natriuretic peptide
NYHA = New York Heart Association
PVC = premature ventricular complex
RFCA = radiofrequency catheter ablation
SHD = structural heart disease
SOO = site of origin
SSA = successful sustained ablation
VT = ventricular tachycardia

in patients with a suspected PVC-induced cardiomyopathy (1–6). The ablation of frequent PVC in a small series of 15 patients with ischemic heart disease (IHD) improved LVEF in comparison with a control group of patients without ablation (7). Similarly, RFCA of PVC improved LVEF and NYHA class in nonresponders to cardiac resynchronization therapy (8). However, the relationship between the degree of clinical benefit and a diagnosis of structural heart disease (SHD) has not been studied. Moreover, patients with suspected PVC-induced cardiomyopathy are followed up for 3 to 6 months after RFCA in most studies; the temporal pattern of improvement after ablation of frequent PVC has not been studied in depth (9).

The aim of the study was to assess the clinical benefit and temporal recovery pattern after ablation of frequent PVC in an unselected group of consecutive patients with LV dysfunction, regardless of the PVC origin or SHD presence and etiology.

Methods

This multicenter, prospective, observational study was conducted from February 2010 to January 2012. A total of 80 consecutive patients with LV dysfunction (defined as LVEF ≤50%) of any etiology and frequent and/or symptomatic PVC accepted for RFCA were included at the four participating centers. Frequent PVC was defined as a burden of more than 4% at baseline 24-h Holter monitoring, which is the lowest reported PVC burden associated with tachycardiomyopathy in the literature (10). No patient was excluded because of the number of PVC morphologies or the presumed site of origin (SOO) based on electrocardiography (ECG) criteria.

Baseline evaluation. A detailed medical and drug history and a blood test, including neurohormonal evaluation (brain natriuretic peptide [BNP] in 3 centers and N-terminal pro-brain natriuretic peptide [NT proBNP] in 1 center) were obtained for all participants. All patients had a 12-lead surface ECG and Holter monitoring prior to the ablation procedure to evaluate the presence of multiple morphologies and to calculate the PVC burden. Baseline echocardiography was performed within the 4 months preceding the RFCA procedure. LVEF was calculated by the Simpson formula (i.e., 3 consecutive beats averaged to minimize distortion generated by PVC). When logistically possible and in the absence of contraindication, a contrast-enhanced cardiac magnetic resonance (ce-CMR) was obtained and analyzed to determine the presence of myocardial scar. Acquisition and post-processing methods are described in the Online Appendix (11).

Ablation procedure. Before the ablation, antiarrhythmic drugs except amiodarone were withdrawn for 5 half-lives. Ablation was guided by the Carto navigation system (Biosense-Webster, Waterloo, Belgium). Intravenous infusion of isoproterenol was used if the patient had no spontaneous PVC at baseline. All PVC morphologies thought to contribute to the LV dysfunction, based on ≥4% burden in Holter monitoring and the operator's clinical judgment during the procedure, were targeted for ablation. A 3.5-mm irrigated-tip catheter (Navi-Star, Biosense Webster) was used for mapping and ablation. Radiofrequency application was guided by activation mapping in 44 patients, pace mapping in 2 patients, and a combination of both techniques in 34 patients. Acute successful ablation was considered when targeted PVC were eliminated and were noninducible after isoproterenol infusion. Patients were monitored for 30 min after the procedure to ensure complete PVC abolition. Programmed stimulation to induce ventricular arrhythmias was not part of the study protocol and was only performed in selected patients, at the operator's discretion. In case of acute successful ablation, amiodarone was discontinued. As the entire population of the study had LV dysfunction, therapy with beta-blocker (90%) and angiotensin-converting enzyme inhibitor was maintained independently of the ablation success.

Follow-up. Patients were attended at an outpatient clinic. Scheduled visits at 1, 6, and 12 months post-ablation included evaluation of functional class and a blood test with BNP determination. In one center, NT pro-BNP was obtained at 3 months.

A 24-h Holter ECG was obtained at 6 and 12 months. Successful sustained ablation (SSA) was defined as the persistent elimination of at least 80% of PVC after a first ablation procedure with no recurrences after 12 months of follow-up. Nonsustained ventricular tachycardia (VT) was defined as VT (>100 beats/min) of ≥3 beats that self-terminates within 30 s. Echocardiography was repeated at 6 and 12 months. Echocardiographic response was defined as an absolute increase in LVEF of ≥5% after RFA, as in clinical trials on CRT implantation and previous PVC ablation series (10,12).

Statistical analysis. Continuous variables are presented as the mean ± SD. BNP and NT-proBNP are presented as the median and interquartile range due to their skewed distributions. Categorical variables are presented as total number and percentages. To compare means of 2 variables, Student *t* test was used (or Wilcoxon when necessary). Proportions were compared using chi-squared or Fisher exact test, as appropriate. Friedman analysis of variance by ranks was used

for repeated measures. Logistic regression analysis was used to study the effects of baseline characteristics in predicting echocardiographic response, acute successful ablation, and SSA. A p value <0.10 was used to screen covariates for inclusion in the multivariate analysis. A backward stepwise selection algorithm was applied to select covariates for inclusion in the multivariate regression model. At each step, the least significant variable was discarded from the model. Odds ratio (OR) and 95% confidence interval (CI) were calculated. Receiver-operating characteristic (ROC) curve analysis was used to evaluate the optimal cutoff value for predicting echocardiographic response. A p value <0.05 was considered statistically significant. Statistical analysis was performed using R software for Windows version 2.15.0 (R Project for Statistical Computing, Vienna, Austria).

Results

Eighty consecutive unselected patients (47 men; mean age: 53 ± 12 years) were included. Follow-up was not available for 3 patients because of 1 noncardiac death, 1 change of residence, and 1 recent diagnosis of disabling neurological disease. Mean LVEF was 34.3 ± 13%, with 22 ± 13% mean PVC burden in the Holter monitoring (Table 1). Before the ablation, an attempt to suppress PVC was ineffective with beta-blocker in 56 patients, amiodarone in 1 patient, and a combination of both in 16 patients.

Dyspnea and palpitations were the dominant presenting symptom in 58 (74%) and 38 (48%) patients, respectively. Only 12 (15%) patients were asymptomatic at the time of ablation. Five patients with SHD had an implantable cardioverter-defibrillator (ICD) for secondary prevention at the time of ablation, 3 of them due to spontaneous sustained VT and 2 because of syncope. Two patients had a pacemaker because of prior atrioventricular block. In all patients without previously diagnosed SHD, IHD was ruled out by coronary angiography or noninvasive stress test before the ablation procedure.

Twenty-seven patients (34%) had previously diagnosed SHD. Seventeen had ischemic heart disease, 2 valvular heart disease, 4 noncompaction cardiomyopathy, and 1 case each of hypertensive cardiomyopathy, peripartum puerperal cardiomyopathy, tetralogy of Fallot, and arrhythmogenic right and left ventricular dysplasia (Table 1). Most patients with previously diagnosed SHD had received that diagnosis before they were considered for PVC ablation, except 2 patients with noncompaction cardiomyopathy in whom a final diagnosis was established by the pre-procedural ce-CMR. Ten of the 17 (59%) ischemic patients had prior myocardial infarction and 7 (41%) additional patients had significant coronary artery disease and prior revascularization without myocardial infarction.

In total, 96 PVCs were targeted for RFCA. Twenty (25%) patients had more than one PVC morphology in the

Table 1 Baseline Characteristics

	No SHD (n = 53)	SHD (n = 27)	All Patients (N = 80)	p Value
Age, yrs	51.5 ± 11.7	56.6 ± 11.4	53 ± 11.8	0.065
Male	25 (47)	22 (82)	47 (59)	0.003
LVEF, %	34.7 ± 7.8	33.5 ± 8.9	34.3 ± 13	0.54
LVESD, mm	44.5 ± 6.8	45.7 ± 7.0	44.9 ± 6.9	0.48
LVEDD, mm	59.3 ± 6.0	61.0 ± 6.9	59.9 ± 6.3	0.21
Treatments, %				
Beta-blocker	92	85	90	0.32
ACEI	81	85	83	0.66
Spironolactone	53	30	51	0.005
Amiodarone	23	19	21	0.67
PVC Holter				
%	18 ± 12	29.8 ± 13.0	22 ± 13	<0.001
n/24 h	17,237 ± 11,109	27,154 ± 16,971	20,326 ± 13,863	0.009
NYHA class				0.19
I	12 (23)	9 (33)	21 (26)	
II	31 (58)	10 (37)	41 (51)	
III	10 (19)	8 (30)	18 (23)	
IV	0	0	0	
Hyperenhancement, % of patients	5.7	33	15	<0.001
BNP, pg/ml	109 (47–340)	107 (85–217)	109 (81–905)	0.94
NP pro-BNP, pg/ml	228 (65–431) (n = 10)	570 (110–938) (n = 7)	259 (97–905) (n = 17)	0.33

Values are mean ± SD, n (%), or median (range).

ACEI = angiotensin-converting enzyme inhibitor; BNP = brain natriuretic peptide; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; NT pro-BNP = N-terminal pro brain natriuretic peptide; NYHA = New York Heart Association; PVC = premature ventricular complex; SHD = structural heart disease.

JACC Vol. 62, No. 13, 2013
September 24, 2013:1195–202

Table 2 Site of Origin of the 96 PVCs Targeted for Ablation and the Number Involving Patients With SHD [in Brackets]

Left Ventricle	Right Ventricle	Epicardium
Outflow tract: 8 left coronary sinus of Valsalva [2] 8 right coronary sinus of Valsalva [1] 3 subvalvular [2]	Outflow tract: 24 septal [2] 15 lateral [2]	Left ventricle summit: 5 [2]
Infarct scars: 8 septal [8] 3 apical [3] 3 lateral [3]	Parahisian: 2 [1]	Cardiac venous system: 6 [2]
Papillary muscle: 5 [5] Mitral annulus: 2 [2]	Tricuspid annulus: 2 [0]	Epicardial scar: 1 [1] Right coronary sulcus groove: 1 [1]

Abbreviations as in Table 1.

baseline Holter monitoring. In 9 of them (4 ischemic and 5 without previous SHD), at least 2 different PVC morphologies were targeted for ablation; only the "dominant" PVC was targeted in the remaining 11 patients. Table 2 shows the site of origin (SOO) of targeted PVCs.

Acute successful ablation was achieved in 68 patients (85%). Complications occurred in 4 patients (5%): 1 uncomplicated hematoma in the puncture site, 1 episode of pericarditis, 1 pulmonary thromboembolism, and 1 episode of periprocedural tamponade resolved without further complications.

Follow-up. Mean follow-up was 11.2 ± 2.4 months. PVC recurred in 15 of 68 patients (22%) with acute successful ablation, in 14 (93%) of them within 6 months. Therefore, SSA was achieved in 53 patients (66%).

Echocardiographic response. In patients with SSA, LVEF improved from 33.7 ± 8% at baseline to 43.8 ± 9.4% and 45.8 ± 10.9% at 6 and 12 months, respectively ($p < 0.05$). Interestingly, most (84 ± 39%) of the benefit was obtained in the first 6 months (Fig. 1). Accordingly, left ventricular end diastolic diameter decreased from 59.5 ± 5.9 mm to 56.3 ± 5.3 mm at 6 months and 54.9 ± 6.1 mm at 12 months ($p < 0.05$). Left ventricular end systolic diameter decreased from 44.4 ± 6.2 mm to 39.9 ± 5.3 mm and 39 ± 6.9 mm at 6 and 12 months, respectively ($p < 0.05$).

There was a close relationship between the percentage of PVC at baseline and echocardiographic response (Fig. 2). When SSA was achieved, a baseline PVC burden ≥13% had

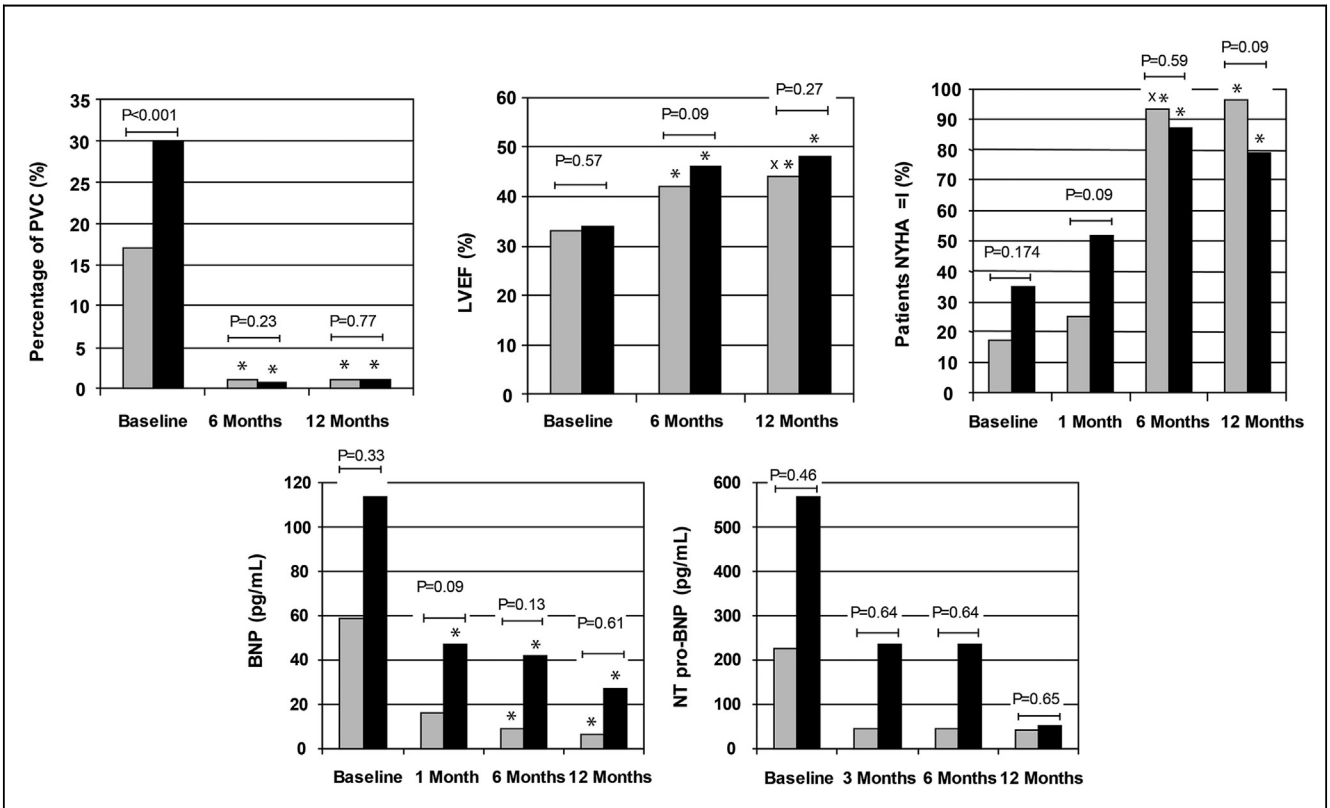

Figure 1 Recovery Pattern After Radiofrequency Ablation In Patients With and Without Previously Diagnosed SHD and With SSA

The temporal recovery pattern of brain natriuretic peptide (BNP)/N-terminal pro brain natriuretic peptide (NT pro-BNP) levels, left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) functional class, and the reduction in premature ventricular complex (PVC) burden is shown. There were no significant differences at baseline except for the PVC burden. Most of the benefit was obtained in the first 6 months. **Gray bars** = no SHD; **black bars** = SHD. *$p < 0.05$ versus baseline. ×$p < 0.05$ versus previous value during follow-up. SHD = structural heart disease; SSA = sustained successful ablation.

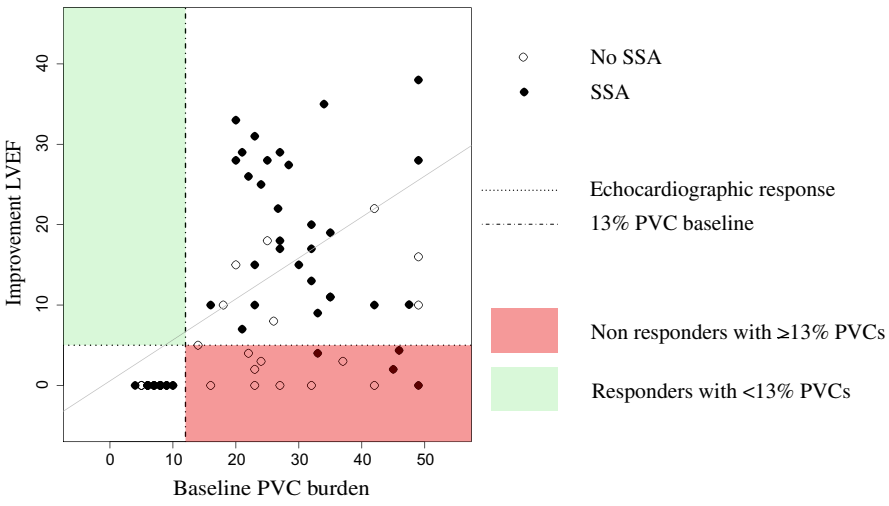

Figure 2 **Echocardiographic Response**

The relationship between the baseline PVC percentage during Holter monitoring and the LVEF improvement during follow-up. **Green** = no patient with a PVC burden <13% improved after radiofrequency ablation. **Pink** = most of the patients without benefit and with a PVC burden ≥13% are without SSA. Abbreviations as in Table 1.

a sensitivity of 100% and a specificity of 85% (area under the curve: 0.87; CI: 0.72 to 1) to predict an absolute increase of at least 5% of LVEF. Echocardiographic response was observed in 88.3% of patients with ≥13% PVC and SSA. In these patients, LVEF improved from 32.6 ± 8.7% at baseline to 48.8 ± 7.2% and 51.9 ± 7.1% at 6 and 12 months, respectively ($p < 0.05$). No patient with <13% PVC at baseline improved after ablation.

At baseline, 29 patients (36%) with ≥13% PVCs met the indication criteria for primary prevention ICD implantation (13). In 20 patients (69%), SSA was achieved and at 6 months post-ablation, none of whom had any ICD indication. In 5 additional patients, the PVC burden was reduced between 50% and 80% from baseline, LVEF improved, and there were no indications for ICD implant at 6 months (n = 3) and 12 months (n = 2). Of the remaining 4 patients, 3 received an ICD and the fourth did not because of comorbidity criteria. No sudden deaths or life-threatening ventricular tachycardias occurred during the entire follow-up.

Neurohormonal response. In patients with SSA, there was a significant reduction in BNP levels from 109 (64 to 242) pg/ml at baseline to 60 (25 to 170), 50 (14 to 130), and 60 (19 to 81) pg/ml at 1, 6, and 12 months, respectively ($p = 0.004$). NT pro-BNP levels showed the same reduction pattern over time from 259 (90 to 907) pg/ml at baseline to 53 (29 to 337), 50 (28 to 330) pg/ml, and 49 (29 to 708) pg/ml at 1, 6, and 12 months, respectively (n = 17; $p = 0.112$) (Fig. 1). Notably, most of the reduction was obtained in the first month.

Clinical response. In patients with SSA, NYHA class improved during the follow-up from only 12 patients (23%) with NYHA I at baseline to 15 (28%), 42 (79%), and 42 (79%) at 1, 6, and 12 months, respectively ($p < 0.001$). Improvement in LVEF was directly related to the temporal pattern of functional recovery.

ce-CMR. A ce-CMR study was available for 59 patients. Hyperenhancement was present in 11 (19%) of them. Eight (66%) of the 12 ischemic patients in whom a ce-CMR was available had hyperenhancement in the ce-CMR study. In patients with hyperenhancement, the mean scar mass was 9.23 ± 8.4 g. There was no significant difference in echocardiographic response rate between patients with or without hyperenhancement (LVEF improvement 12 ± 7.6% and 9.6 ± 12.3%, respectively; $p = 0.56$). Patients with hyperenhancement had a greater baseline PVC burden (30 ± 13.7 vs 17.5 ± 10.7; $p = 0.001$) and a greater absolute reduction of PVC percentage after SSA (29.8 ± 11.9 vs 15.5 ± 10.6; $p = 0.003$). Interestingly, the SOO was not related to the hyperenhanced areas in 7 (54%) of the 13 PVCs ablated in patients with scar in the ce-CMR.

Previously diagnosed SHD. There is an association between previously diagnosed SHD and LV origin (78% of the patients with a previously diagnosed SHD had a LV site of PVC origin vs 26% in patients without; $p < 0.001$). In patients with previously diagnosed SHD, the PVC burden was significantly higher at baseline (Fig. 1) and the reduction of PVC after SSA was more pronounced as compared to patients without SHD (absolute reduction of PVC percentage: 16 ± 11% in patients without SHD, 28 ± 13% in patients with SHD; $p = 0.002$). There was no difference in echocardiographic response between patients with known SHD and idiopathic LV dysfunction (mean absolute LVEF improvement during follow-up, 13.5 ± 11.8% vs 12 ± 13%, respectively; $p = 0.691$). Accordingly, there was no difference in neurohormonal response (mean improvement in BNP levels: 56 [5 to 143] pg/ml without SHD vs 87 [33 to

JACC Vol. 62, No. 13, 2013
September 24, 2013:1195–202

Table 3 Echocardiographic, Neurohormonal, and Clinical Response After Ablation in Patients With and Without Successful Sustained Ablation

	SSA (n = 53)	No SSA (n = 27)	p Value
LVEF improvement after RFCA, %	12.6 ± 12.4	5.1 ± 6.7	0.007
BNP reduction after RFCA, pg/ml	87 (20 to 131)	22 (−17 to 37)	0.14
NP pro-BNP reduction after RFCA, pg/ml	123 (44–368)	25 (−98 to 120)	0.12
Patients with NYHA II or higher at baseline and a decrease of 1 or more NYHA class after RFCA	36 (94)	11 (60)	0.003

Values are mean ± SD, median (95% confidence interval), or n (%).
RFCA = radiofrequency catheter ablation; SSA = sustained successful ablation; other abbreviations as in Table 1.

130] pg/ml SHD, p = 0.79; mean improvement in NT pro-BNP levels: 63 [36 to 240] pg/ml without SHD vs 183 [117 to 340] ml SHD; p = 0.655) or in clinical improvement during follow-up after SSA (symptomatic patients with a decrease of at least 1 category of NYHA class during follow-up: 27 (96%) without SHD vs 9 (90%) with SHD; p = 0.462).

Unsuccessful ablation. In 27 patients (34%), SSA was not achieved; the ablation attempt was unsuccessful in 12 patients (15%) and PVC recurred during follow-up in 15 (19%) additional patients. Recurrent PVC was different than that previously ablated in 2 patients (17%) without SHD and in 2 patients (67%) with SHD.

Patients without SSA showed less improvement in LVEF, rate of clinical response, and BNP/NT pro-BNP reduction (Table 3). However, 7 patients with no SSA were clinical responders (Fig. 2). In 5 of these patients, PVC recurred but the PVC burden was decreased by 50% to 80%. In the other 2 patients, PVC elimination was obtained with antiarrhythmic drugs. In 4 patients, a second ablation procedure was performed and 2 of them recurred.

Patients without SSA more frequently had nonsustained VT during the follow-up Holter monitoring (48% vs 11%; p = 0.001), although none of the patients had life-threatening arrhythmias.

Age, more than 1 PVC morphology at baseline, and epicardial origin were associated with failure to achieve SSA. In the multivariate analysis, only epicardial origin independently predicted failure in achieving SSA (OR: 4.2; 95% CI: 1.1 to 16.4; p = 0.042). Age, more than 1 PVC morphology at baseline, and epicardial origin were associated with a failure to achieve acute ablation success. Only epicardial origin (OR: 6.9; 95% CI: 1.46 to 33.3; p = 0.015) and the presence of more than 1 PVC morphology in the baseline Holter monitoring (OR: 6.2; 95% CI: 1.3 to 29.8; p = 0.022) were independent predictors in the multivariate analysis (Online Tables 1 to 3).

Predictors of echocardiographic response. Table 4 shows the univariate and multivariate analysis for the prediction of echocardiographic response. Only SSA and baseline PVC percentage predicted response. The other variables analyzed were suspected SOO (right vs. left), epicardial origin, QRS width, SHD etiology, and scar size in the ce-CMR. In addition, neither the epicardial origin (3 [9%] in responders vs 1 [5%] in nonresponders; p = 0.97) nor the QRS width (170 ± 19 ms in responders vs. 175 ± 19 ms in nonresponders; p = 0.41) were associated with the echocardiographic response in the subgroup of patients with SSA.

Discussion

The present study describes the neurohormonal, echocardiographic, and clinical benefit, and the recovery pattern of consecutive patients with depressed LVEF and frequent PVC submitted for ablation, regardless of the presence of previously diagnosed SHD. This is also the first series to describe in depth the influence of PVC recurrences in outcomes and timing, with 93% of recurrences occurring in the first 6 months. The ablation complexity of some PVCs, depending on SOO, probably explains why SSA was achieved in only two-thirds of patients, along with a perhaps higher recurrence rate in an unselected patient population with a large proportion of patients having epicardial PVCs. As a similar benefit was obtained irrespective of known

Table 4 Predictors of Echocardiographic Response, Univariate and Multivariate Models

			Univariate		Multivariate	
	Response	No Response	OR (95% CI)	p Value	OR (95% CI)	p Value
Male, %	71.4	42.8	3.33 (1.29–8.92)	0.01		
Age, yrs	53.7 ± 12.3	52.6 ± 11.4	1.01 (0.97–1.05)	0.67		
Baseline PVC burden, %	29 ± 9.7	15.4 ± 13	1.11 (1.05–1.17)	<0.001	1.12 (1.06–1.18)	<0.001
QRS width, ms	170 ± 19	174 ± 18	0.99 (0.96–1.01)	0.33		
Location, left ventricle, %	44.7	81.8	1.02 (0.45–2.81)	0.81		
Location, epicardial, %	20.0	11.4	1.68 (0.51–5.63)	0.4		
SSA, %	76.2	57.1	2.40 (0.90–6.40)	0.08	3.82 (1.09–13.32)	0.036
SHD, %	40.5	28.6	1.70 (0.65–4.43)	0.28		
Scar size, g	1.56	1.57	0.99 (0.89–1.11)	0.99		

Values are % or mean ± SD.
OR = odds ratio; other abbreviations as in Tables 1, 2, and 3.

SHD, the distinction between a "PVC-induced" cardiomyopathy and a "PVC-worsened" cardiomyopathy does not seem to be essential in selecting patients for PVC ablation. In contrast, a higher baseline PVC burden was associated with neurohormonal, echocardiographic, and clinical benefit and may be used to select patients. An important finding of the study was the consistent temporal pattern of improvement for all heart failure parameters; an early improvement of BNP/NT pro-BNP levels, functional class, and LVEF was observed and persisted after 6 months of follow-up.

PVC-induced or PVC-worsened cardiomyopathy. Although there are several reports of reversible cardiomyopathy after PVC ablation in patients with frequent PVC (1–8), most studies have included only patients with suspected PVC-induced cardiomyopathy; patients with known SHD have been systematically excluded. The present study was the first to assess PVC ablation outcomes in unselected patients with frequent PVCs and depressed LVEF. The findings are clinically important because PVCs are frequently observed in patients with SHD (14) and because a reversible "PVC-worsened" cardiomyopathy is a concept not yet deeply described and widely accepted. As a result, many of these patients are not considered candidates for RFCA. The present study suggests that they should be.

The improvement in LVEF observed in both groups, with and without known SHD, is comparable to that reported in previous studies (3,4) in selected patients with PVC-induced cardiomyopathy. One-third of patients had previously diagnosed SHD and their LVEF improvement did not differ from that of patients with suspected PVC-induced cardiomyopathy. That finding is consistent with a report of significant LVEF improvement after ablation of frequent PVC in a series of 15 patients with previous myocardial infarction (7). The authors suggested that the depressed LV function is at least partly due to a reversible cardiomyopathy in patients with more than 5% PVC at baseline, despite the presence of scar tissue. The present results support this hypothesis in a more heterogeneous group of patients with heart diseases of different etiologies. Interestingly, patients with previously diagnosed SHD as well as patients with hyperenhancement in the CMR study had a significantly higher PVC burden at baseline and a greater reduction of PVC percentage after SSA. This phenomenon could be explained in part by a referral bias (i.e., patients without a diagnosis of SHD are likely referred earlier for PVC treatment). As PVC burden is an independent predictor of response after ablation, this finding may explain a similar benefit after PVC ablation in patients with and without SHD as well as the lack of influence of the amount of scar in the response.

On the other hand, the small percentage of patients with myocardial scar is in accordance with a previous report by Sarrazin et al. (7), in which patients with myocardial infarction and frequent PVC had a smaller scar area in the ce-CMR than patients without PVC with similar LVEF. This finding suggests that a component of PVC-worsened LV dysfunction is present. Further studies with a higher number of patients having scar on ce-CMR are needed to establish its influence on response after frequent PVC ablation.

Predictors of response. In the present study baseline PVC percentage predicted response to RFCA. The PVC burden necessary to induce or worsen LV dysfunction is not clearly defined. A burden as low as 4% was found to be associated with cardiomyopathy (10). However, in another study the majority of patients with PVC-induced cardiomyopathy who improved after ablation had more than 10% PVC at baseline (15). In the present study, the optimal cutoff value in patients accepted for ablation was $\geq$13% PVC at baseline to predict LVEF improvement of at least 5%. Importantly, no patient with less than 13% baseline PVCs improved after ablation. This is in line with the study of Baman et al. (15), who reported that the lowest PVC burden resulting in a reversible cardiomyopathy was 10% in patients with PVC-induced cardiomyopathy.

Previous studies showed that an epicardial PVC origin as well as the QRS width of PVC were predictors of a reversible PVC-induced cardiomyopathy (16). In the present study, neither right versus left SOO, nor epicardial origin, nor QRS width were independent predictors of response. Although the SOO (epicardial origin) was associated with a lower rate of SSA, only the SSA was an independent predictor of response, suggesting that the lack of PVC burden reduction is the main variable to be taken into account, rather than the SOO. Therefore, repeated Holter monitoring could be recommended to check for SSA and correctly interpret the response after ablation. Notably, any recurrences are most likely to occur in the first 6-month period.

Finally, despite ablation of only the "dominant" PVC in 11 of the 20 patients with multiple morphologies at baseline, this was not an independent predictor of SSA. This observation suggests that the elimination of all PVC morphologies may not be necessary.

ICD implantation. As a consequence of improvement in heart failure parameters and the increase in LVEF, all patients with $\geq$13% baseline PVC burden and SSA meeting the indication criteria for primary prevention ICD implantation prior of RFA had no such indication 6 months after ablation. No sudden deaths or life-threatening ventricular arrhythmias occurred in these patients during the 6-months waiting period for re-evaluation nor during the entire follow-up. In view of these results, and taking into account that the 84 $\pm$ 39% of the LVEF improvement was observed in the first 6 months after ablation, the 6-month reevaluation interval after successful ablation seems to be a safe approach. Whether an early evaluation for the presence of PVC recurrences should be done remains to be determined. Larger studies are needed to determine the length of the period for which ICD implantation can be withheld safely.

Study limitations. The main limitation of this study is the absence of a control group. A 24-h Holter monitoring may be insufficient to assess the exact PVC burden before and

after ablation, due to the day-to-day variability of ectopy. Use of antiarrhythmic drugs in patients without acute successful ablation may affect the interpretation of the results, although only two patients reached ≥80% reduction of baseline PVC burden. The electrophysiological mechanism of the ventricular arrhythmia was not systematically studied, but could influence the ablation strategy and recurrences if the PVC were related to scarring. Finally, although the presence of scar seems not to be essential in selecting patients for PVC ablation, it might influence the degree of reverse remodeling. We cannot exclude the possibility that LV dysfunction does not improve after PVC elimination in patients with significant SHD and a large myocardial scar. Further studies with a higher number of patients having large scars on ce-CMR are needed to establish any influence on response after frequent PVC ablation.

Conclusions

Ablation of frequent PVC is associated with a progressive neurohormonal, structural, and functional improvement in unselected patients with depressed LVEF, regardless of a potential PVC-induced or PVC-worsened cardiomyopathy. Improvement in LVEF was related to the baseline PVC burden and the persistence of acute ablation success. Given the magnitude of the obtained benefit and its consistency in unselected patients, all patients with depressed LVEF should be evaluated for the presence of frequent PVCs, especially those meeting criteria for primary prevention ICD implantation, as the benefit might influence clinical decisions.

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Key Words: premature ventricular complexes ■ radiofrequency catheter ablation ■ structural heart disease.

APPENDIX

For more details on the methods of this study, please see the online version of this paper.