Premature ventricular contractions in patients with an implantable cardioverter defibrillator cardiac resynchronization therapy device: Results from the *UMBRELLA* registry

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ABSTRACT

Background: Premature ventricular contractions (PVC) are known to reduce the percentage of biventricular (BiV) pacing in patients with cardiac resynchronization (CRT), decreasing the clinical response. The aim of this study was to evaluate the prevalence of a high PVC burden, as well as therapeutic action (pharmacotherapy, catheter ablation or device programming), in a large CRT implantable-defibrillator (CRT-D) population.

Methods: Patients with a CRT-D device from the *UMBRELLA* multicenter prospective remote monitoring registry were included. The PVC count was collected from each remote monitoring transmission. Patients were divided into two high ($\geq$1 transmission $\geq$200/$\geq$400 PVC/h, respectively) and one low (all transmissions <200 PVC/h) PVC count groups. The PVC burden following a high PVC count transmission was calculated.

Results: Of 1268 patients, 135 (11%) and 43 (3.4%) presented high PVC count ($\geq$200/$\geq$400 PVC/h, respectively). The majority of patients in the high PVC groups were not treated (61 [79%] and 32 [74%], respectively). Considering the untreated patients in the high PVC groups, median PVC/h was 199 (interquartile range [IQR]: 196) and 271 (IQR: 330), respectively. The PVC burden (proportion of time with PVC/h $\geq$ 200/$\geq$400) was 40% (IQR 70) and 29% (IQR 59), respectively.

Conclusion: A significant proportion of CRT-D patients presented a high PVC count, however, few received treatment. In the untreated patients with a high PVC count, the PVC burden during follow-up varied substantially. Several consecutive recordings of a high PVC count should be warranted before considering therapeutic action such as catheter ablation.

1. Introduction

Cardiac resynchronization therapy (CRT) reinstates

atrioventricular, interventricular, and intraventricular electromechanical synchrony, causing improved left ventricular (LV) function, reduced mitral regurgitation, and induced reverse LV remodeling, which clinically leads to reduced heart failure (HF) hospitalization and all-cause mortality [1,2]. Nevertheless, after two decades since its introduction, one-third of patients do not clinically respond and up to a half do not present reverse LV remodeling. The causes of this non-response are multifactorial and may involve pre- peri- and post-implant factors such as patient selection, LV lead positioning, device programming, and cardiac arrhythmias [3]. With regards to the latter, atrial and ventricular arrhythmia are known to reduce

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Abbreviations: BiV, Biventricular; CRT, Cardiac resynchronization therapy; HF, Heart failure; ICD, Implantable cardioverter-defibrillator; LV, Left ventricle; PAC, Premature atrial complex; PVC, Premature ventricular complex.
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the capability of the CRT device to deliver effective biventricular (BiV) pacing (>98%), thereby increasing the risk of non-response [4]. A subanalysis of the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) demonstrated a clear relationship between the burden of atrial and ventricular premature contractions (PAC; PVC) and low percentage of BiV pacing which in turn was linked to less reverse remodeling, and increased HF, death and ventricular tachyarrhytmias. Interestingly, the negative effects of PAC and PVC on CRT response were observed even at a relatively low burden (0.1%–1.5%) [5]. Furthermore, the presence of fusion and pseudofusion beats, often seen with atrial fibrillation (AF) and PVC triggered LV pace algorithms, can also decrease response to CRT despite an (incorrectly) elevated percentage of BiV pacing. It is therefore important to identify CRT patients with a high PVC burden in order to initiate appropriate therapy. In patients without structural heart disease, catheter ablation has been shown to be superior when compared to pharmacotherapy in PVC suppression [6], however, comparative data on CRT patients is lacking, although one study found improved CRT efficacy in non-responders with high PVC burden following catheter ablation [7].

In this study, we analyzed the prevalence of high PVC count and PVC burden in patients with CRT implantable-defibrillator (CRT-D) devices. Treatment of PVC, pharmacotherapy (initiation/uptitration of betablockers or amiodarone), catheter ablation or device programming, were also evaluated.

1.1. Methods

This multicenter prospective observational study was conducted within the framework for observational research provided by the UMBRELLA registry (Incidence of arrhythmias in the Spanish population with a Medtronic [Medtronic, Inc., Minneapolis, MN, USA] ICD. UMBRELLA is a voluntary registry promoted by Medtronic that includes patients with Medtronic ICD, capable of remote monitoring (i.e. integrated in CareLink® System, Medtronic), implanted according to current clinical guidelines. Several analyses regarding the incidence of arrhythmias and ICD therapies in this population have been published previously [8–11]. The ethical committees of all participating centers approved the study protocol and all patients provided informed consent. All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The study population included all patients from the UMBRELLA registry with a CRT-D device. Baseline patient characteristics were extracted from the registry database. The PVC count was obtained from each remote monitoring transmission, which in a Medtronic device is expressed as mean PVC/h throughout the transmission time period. The device defines PVC as any ventricular sensed event that follows another ventricular event without an intervening atrial event (DDD mode); or if a ventricular sensed event has an R-R interval <69% of the average of the intervals of the four most recent consecutive ventricular events (VVI mode). Furthermore, the PVC count is expressed as PVC singles (1 beat) and runs (2–4 beats) [12]. In all instances the PVC count in this study represents the sum of PVC singles and runs as recorded in each remote monitoring transmission. Patients were divided into two high (≥1 transmission of ≥200 PVC/h [≈5% PVC burden]; or ≥400 PVC/h [≈10% PVC burden]) and one low (all transmissions <200 PVC/h) PVC count groups. For the high PVC groups the PVC burden was expressed as: a) percentage of time in ≥200/≥400 PVC/h since the first ≥200/≥400 PVC/h transmission; b) median PVC/h since the first ≥200/≥400 PVC/h transmission. Following this, additional data (in forms of a questionnaire), including PVC morphology and treatment of PVC (pharmacotherapy [initiation/uptitration of betablockers or amiodarone], catheter ablation, device programming) in the high PVC groups were requested from the collaborating investigators.

1.2. Statistical analysis

Normality of data distribution was tested with the Kolmogorov-Smirnov test or Shapiro-Wilk test. Continuous variables were expressed as mean ± standard deviation (SD) in case of normal distribution or as median and interquartile range (IQR) when data was skewed or non-normal. Comparisons where made using the Student's t-test for independent samples or the Mann-Whitney U Test, depending on their distribution. Categorical variables were expressed as absolute frequencies and percentages and compared using the chi-square test or Fisher's exact test, were appropriate. Post hoc tests for multiple comparisons with Bonferroni adjusted alpha levels were performed when appropriate. A Kaplan-Meier graph was constructed for survival comparison between the treated and non-treated high PVC burden patients, with the log-rank for significance testing. A P-value of <0.05 was considered significant for all statistical tests. SPSS (version 21.0) software was used for statistical analysis (SPSS, Inc, Chicago, IL, USA).

2. Results

A total of 1268 patients with a Medtronic CRT-D device implanted between March 2007 and May 2017 were included in the study. The first and last remote transmission, were on October 2007 and June 2017, respectively, and the median time between transmissions were 40 days (IQR: 64). Median follow-up for the high (≥200 PVC/h) and low PVC groups were 31 months (IQR: 30) and 38 months (IQR: 27), respectively ($P = 0.81$). Mean age was 70 ± 11 years, and the majority of patients were male (78%) with dilated nonichemic cardiomyopathy (50%), in New York Heart Association (NYHA) functional class II or III (88%) and LV ejection fraction (LVEF) < 30% (73%). Most patients were in sinus rhythm at implant (67%), the rest presenting AF (21%) and paced rhythms (12%).

When stratified by PVC count, 135 (11%) patients presented ≥1 transmission of ≥200 PVC/h. When compared with the other 1133 patients with no transmission of ≥200 PVC/h, there were no significant differences in baseline characteristics between the groups, apart from a higher proportion of patients with nonischemic cardiomyopathy and valvular heart disease in the high PVC group (Table 1). Out of the 135 patients from the high PVC group (≥200 PVC/h), additional data regarding therapeutic interventions and PVC morphology was available in 77 and 39 patients, respectively. The majority of PVC where of left bundle branch morphology (68%) and had an inferior frontal plane axis (48%). In most patients in the high PVC group, no therapeutic action was taken (79%), with pharmacotherapy (consisting of initiation or titration of a betablocker or initiation of amiodarone) being utilized in 20% of patients (Table 2). Only 1 patient underwent catheter ablation of PVC and in no instances device reprogramming was performed. Considering the patients (n = 61) in the high PVC group (≥200 PVC/h) that were not treated, the median PVC/h of all subsequent transmissions following the first ≥200 PVC/h transmission was 199 PVC/h (IQR: 196) with a total range of: 12–1436 PVC/h. The PVC burden (median time spent in ≥200 PVC/h) following the first ≥200 PVC/h transmission was 40% (IQR: 70) with a total range of 0.1–100% (Fig. 1A). Treated patients in the high PVC group (≥200 PVC/h) presented a median PVC/h of 199 PVC/h (IQR: 102) with a total range of: 29–1214 PVC/h. There was no difference in PVC burden (median time spent in ≥200 PVC/h) or median PVC/h when comparing treated and untreated patients from the high PVC group

Table 1
Baseline characteristics of the study population stratified by premature ventricular contraction (PVC) count.

	Low PVC count (<200 PVC/h) (n = 1133)	High PVC count (≥200 PVC/h) (n = 135)	P
Age (years)	70.8 ± 10.8	70 ± 11.6	0.41
Time since diagnosis (years)	9.1 ± 7.6	10 ± 6.9	0.37
Males, n (%)	874 (77.1)	110 (81.5)	0.25
Primary prevention, n (%)	954 (84.2)	110 (81.5)	0.42
Hypertension, n (%)	692 (63.4)	83 (62.4)	0.83
Smoking, n (%)	294 (29.9)	32 (28.8)	0.81
Dyslipemia, n (%)	569 (55.7)	67 (55.8)	0.97
Stroke, n (%)	75 (7.7)	7 (5.8)	0.47
Cardiomyopathy etiology, n (%)			<0.001[a]
Ischemic	469 (41.4)	62 (45.9)	0.11[b]
Nonischemic	584 (51.5)	53 (39.3)	0.01[b]
Hypertrophic	15 (1.3)	0 (0)	0.09[b]
Valvular	35 (3.1)	14 (10.4)	<0.001[b]
Rhythm at implant, n (%)			0.97[a]
Sinus	720 (66.8)	89 (67.9)	
Atrial fibrillation	230 (21.3)	27 (20.6)	
Paced	128 (11.9)	15 (11.5)	
LVEF, n (%)			0.25[a]
<30%	825 (73.1)	95 (70.4)	
31—35%	211 (18.7)	22 (16.3)	
36—40%	63 (5.6)	12 (8.9)	
41—50%	30 (2.7)	6 (4.4)	
NYHA class, n (%)			0.53[a]
Class I	45 (4.2)	6 (4.7)	
Class II	452 (42.5)	60 (47.2)	
Class III	541 (50.9)	60 (47.2)	
Class IV	25 (2.4)	1 (0.8)	

Values are n (%), mean ± SD, or median (interquartile range).
 [a] Overall P value for comparisons.
 [b] P value for post hoc comparison. NYHA = New York Heart Association functional class; LVEF = left ventricle ejection fraction.

Table 2
Characteristics and therapeutic intervention of patients with high PVC count (≥200 PVC/h).

Multiple morphologies[a]	17 (43.6)
Frontal plane axis[a]	
Inferior	13 (48.1)
Superior	6 (22.2)
Left	5 (18.5)
Right	3 (11.1)
Morphology[a]	
Left bundle branch block	18 (66.7)
Right bundle branch block	9 (33.3)
Therapeutic intervention[b]	
No therapeutic intervention	61 (79.2)
Pharmacotherapy (beta-blocker or amiodarone)	15 (19.5)
Catheter ablation	1 (1.3)
Device reprogramming	0 (0)

All values expressed as n (%).
 [a] Additional data regarding PVC morphology was available in 27—39 patients from the high PVC count group.
 [b] Additional data regarding therapeutic interventions was available from a total of 77 patients from the high PVC count group.

(≥200 PVC/h) (P = 0.88 and P = 0.89, respectively). Furthermore, there was no difference in VT/VF occurrence during follow-up for those treated and not treated (P = 0.21). At the point of last remote transmission 67.1% of the patients were alive and there was no difference in survival when comparing patients in whom a therapeutic action to lower the PVC count had been taken with those in whom no therapeutic action was taken (log-rank P = 0.6) (Fig. 2).

Using a higher cut-off of ≥400 PVC/h, 43 (3.4%) patients where identified from the 135 patients with a PVC burden of ≥200 PVC/h. Considering the patients (n = 32) with a higher PVC burden cut-off (≥400 PVC/h) that were not treated, the median PVC/h of all subsequent transmissions following the first ≥400 PVC/h transmission was 271 PVC/h (IQR: 330) with a total range of: 43—1436 PVC/h. The PVC burden (median time spent in ≥400 PVC/h) following the first ≥400 PVC/h transmission was 29% (IQR: 59) with a total range of 1.4—100% (Fig. 1B).

3. Discussion

This study evaluated PVC burden in patients with a CRT-D device in a large Spanish multicenter prospective registry. We found that 11% of the all patients with a CRT-D device presented at least one remote transmission recording of a high PVC count (≥200 PVC/h). In this group of patients, the median PVC and PVC burden varied substantially and noteworthy, in the vast majority of these patients, no therapeutic action to reduce PVC burden was taken.

A high percentage (>98%) of biventricular (BiV) pacing is necessary in order to derive maximum benefit from CRT [4]. Both PAC and PVC are known to proportionally reduce BiV pacing with diminished clinical response to CRT as a result. Effective identification and treatment of PVC in CRT patients is therefore of interest. Pharmacotherapy is usually first-line treatment and has been shown to modestly suppress PVC in patients without structural heart disease [13], although there is no data in patients with structural heart disease i.e. CRT patients, as in this study. Furthermore, amiodarone has several important side effects and most CRT patients are already on maximum dose of beta-blocker therapy, making catheter ablation in many of these patients the only viable therapeutic option. Catheter ablation of PVC in CRT patients has so far only been evaluated by one study which included 65 CRT non-responder patients with >10,000 PVC/24h [7]. Acute and long-term success was 91% and 88% at one-year follow-up, and 2 patients experienced procedure-related major complications. During follow-up, there was a significant improvement in LVEF, LV end-systolic diameter and NYHA functional class. The average BiV pacing increased from 76% to 98% following PVC ablation.

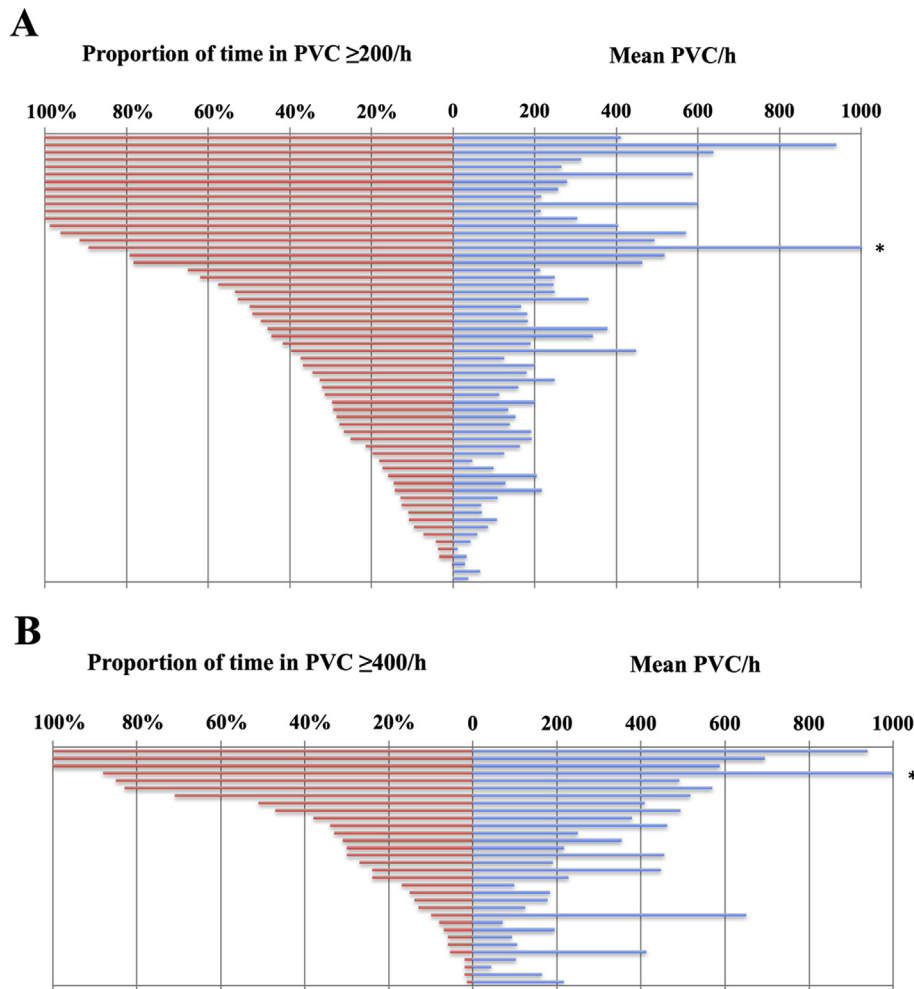The exact prevalence of high burden PVC in patients with CRT

Fig. 1. Mirror bar charts of the premature ventricular contractions (PVC) burden in patients with ≥1 remote transmission of a high premature ventricular contraction (PVC) count (≥200 PVC/h in **A**; ≥ 400 PVC/h in **B**). Each horizontal bar represents a patient with proportion of time in ≥200/≥ 400, respectively in red and mean PVC in blue. *Mean PVC = 1436 PVC/h.

device is unknown and obviously depends on the cut-off being used. A MADIT-CRT subanalysis, 15% of patients were found to have >5000 PVC during a 24-h period at the study enrollment, similar to what was observed in our study (11% of >200PVC/h) [14]. Despite the relatively high prevalence of high PVC burden in our study, in the vast majority of patients (n = 61; 79%) no therapeutic action was taken and catheter ablation was performed in only 1 (1,6%) patient. The reason for such a high proportion of untreated patients is unknown to us but one may assume that a high PVC count was in many instances not noticed by the caring physician (electrophysiology specialist in the *UMBRELLA* registry), despite repeated transmissions with high PVC count in several of the patients (28% patients presented a PVC count ≥200 PVC/h in >50% of their transmissions). Since our study is based on a remote transmission CRT-D registry one may assume that a significant proportion of patients were only remotely followed-up for most of the time, and given that a high PVC count is not classified as a *CareAlert*® (Medtronic) this may easily go unnoticed. Irrespectively of the cause for the untreated PVC we hope that our observations will prompt physicians to be more attentive to the PVC count during CRT patient follow-up and to take therapeutic action, even when the PVC count is relatively low, since this has been reported to improve the CRT response [7]. Furthermore, an implementation of a *CareAlert*® for a high PVC count in the *Carelink*® system online

platform would obviously make high PVC count detection easier.

3.1. Impact of PVC burden in the clinical setting

Pharmacotherapy probably has a limited role in many CRT patients with high PVC burden and in our study the initiation/uptitration of betablockers or initiation of amiodarona did not significantly reduce the PVC burden. As expected, given that PVC burden was not reduced by pharmacotherapy, no difference in VT/VF episodes or survival was observed when comparing treated and untreated high PVC burden patients. Therefore, catheter ablation should probably be considered in most of these patients, although our analysis did not cover this topic since only 1 patient underwent ablation. However, we found that the PVC burden (time spent in ≥200 PVC/h) and mean PVC varied substantially in patients with one high PVC count recording (≥200 or ≥400 PVC/h). For instance, of the untreated patients with one high PVC count recording, a significant proportion (51% and 39% for the ≥200 PVC/h and ≥400 PVC/h groups, respectively) presented a low PVC burden (<200 PVC/h) in all subsequent remote transmission. Therefore, it would have been difficult to be treat many of these patients invasively since a relatively high PVC density is desired for effective activation mapping during the electrophysiology study and for evaluation of the ablation effectiveness. Although several studied have evaluated
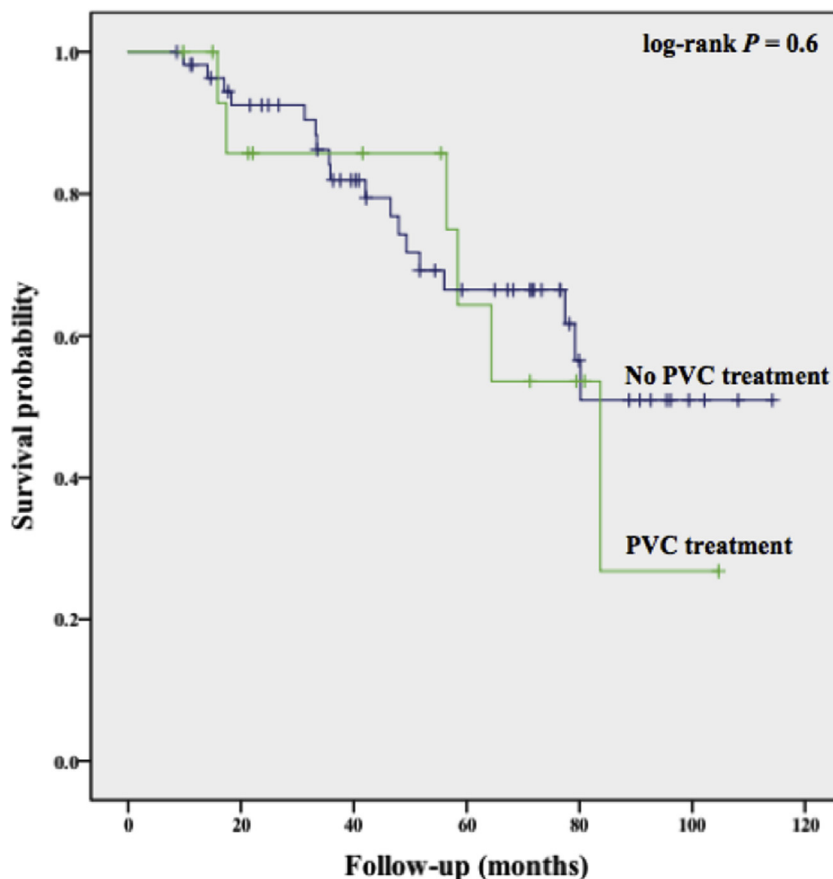
Fig. 2. Kaplan-Meier estimates of survival probability in the treated and untreated patients with high premature ventricular contractions (PVC) (≥200 PVC/h).

the circadian variability patterns of PVC, usually during a 24-h period, to the best of our knowledge there is little data on long term burden variability [15,16]. Only recently, one retrospective study in patients with PVC ≥5% and normal LVEF, 44% presented a reduction to <1% PVC burden during follow-up [17]. The variability in PVC burden in CRT patients is likely multifactorial, including factors such as HF status (e.g. reverse remodeling from the CRT itself), HF medication changes and acute disease such as ischemic events [18,19]. Consequently, a high PVC count does not necessary mean that the patient will continue with a high enough PVC burden to be suitable for catheter ablation. Several consecutive high PVC recordings seem a reasonable requisite before considering catheter ablation.

3.2. Limitations

The study analysis was based on the CRT-D device automated PVC count algorithms hence no manual analysis was carried out. Therefore, the PVC count may have been overestimated in the case of coexistent AF or intermittent atrial undersensing. Also, the number of PVC in a PVC *run* (2–4 beats) is not specified and was for practical reasons regarded as 3 PVC for the data analyses. Another limitation is the lack of accurate data on the percentage of BiV stimulation, which is commonly overestimated due to the *Ventricular Sense Response*® (VSP) feature in Medtronic CRT-D devices [12]. Both the percentage of BiV stimulation and on the VSP feature would have been of interest in order to assess the PVC impact on CRT delivery. However, PVC burden has already been clearly linked to reduced BiV pacing and was not the purpose of this study [5,6]. Furthermore, the exact doses of beta-blocker used in patients who

were treated for high PVC burden was not known and some patients may not have received the maximum tolerated dose. Together with a relatively low number of patients (n = 11) it is possible that the effect of pharmacotherapy on PVC reduction was not properly detected in this study. Data on clinical outcome, including timing and progression of cardiomyopathy, in relation to the CRT implant and PVC burden was not available to us. Hence it was not possible to analyze the relationship between PVC burden estimates and impact on BiV pacing percentage and patient clinical status. However, we still believe our findings to be of clinical interest, since our series represent current clinical practice in unselected CRT patients, highlighting a significant PVC burden variation over time, even though the reasons for this cannot be elucidated in this study.

4. Conclusion

In a large Spanish multicenter registry of remote transmissions of CRT-D patients, a significant proportion presented a high PVC count. However, in only a minority of cases a therapeutic action to reduce the PVC burden was taken. Careful attention of the PVC count during patient follow-up with subsequent treatment when appropriate is necessary in order to improve CRT response. Moreover, in the untreated patients with a recording of a high PVC count, mean PVC count and burden varied substantially, for which reason several consecutive recordings of a high PVC count should be warranted before considering therapeutic intervention such as catheter ablation.

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None.

Declaration of competing interest

None.

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