

SYSTEMATIC REVIEW ARTICLE

Predictors of Left Ventricular Ejection Fraction Improvement after Radiofrequency Catheter Ablation in Patients with PVC-Induced Cardiomyopathy: A Systematic Review

Farbod Z. Tajrishi¹, Mohammad H. Asgardoost², Amirhossein S. Hosseinpour³, Alipasha Meysamie⁴ and Ali Vasheghani-Farahani^{5,6,*}

¹School of Medicine, Babol University of Medical Sciences, Babol, Iran; ²Iranian Student Society for Immunodeficiencies, Students' Scientific Research Center, Tehran University of Medical Sciences, Tehran, Iran; ³School of Medicine, Tehran University of Medical Sciences, Tehran, Iran; ⁴Community and Preventive Medicine Department, Tehran University of Medical Sciences, Tehran, Iran; ⁵Cardiac Primary Prevention Research Center (CPPRC), Tehran Heart Center, Tehran University of Medical Sciences Tehran, Iran; ⁶Electrophysiology Department, Tehran Heart Center, Tehran University of Medical Sciences, Tehran, Iran

Abstract: Background: Frequent premature ventricular contractions (PVC) can result in PVC-induced cardiomyopathy (PVC-iCMP), leading to reduced Left Ventricular Ejection Fraction (LVEF) that can be improved by radiofrequency catheter ablation (RFCA). We performed a systematic review to determine the variables predicting LVEF improvement after RFCA in PVC-iCMP.

Methods: We developed a “population, intervention, outcome and predictive factors” framework and searched MEDLINE, Embase, Cochrane Library, Cochrane Collaboration and Cochrane Database of Systematic Reviews (CDSR) for full-text, peer-reviewed publications. These publications addressing predictive factors of LVEF improvement showed $\geq 5\%$ improvement only if deemed significant by the respective study, $\geq 10\%$ or $\geq 50\%$ after RFCA ablation in patients with PVC-iCMP with no type/date/language limitation until the end of 2017.

Results: Our initial search yielded 2226 titles, 1519 of which remained after removing the duplicates. Finally, 11 articles - 2 cohorts, 7 quasi-experimental studies, 1 case-control and 1 meta-analysis- were included. Sustained successful ablation, higher baseline PVC burden, LVEF, QRS duration, post-PVC systolic blood pressure rise and post-PVC pulse pressure change, the absence of an underlying cardiomyopathy, younger age, and variability of the frequency of PVCs during the day and lower left ventricular end-diastolic diameter (LVEDD) have been suggested as predictive factors for LVEF improvement in patients with PVC-iCMP.

Conclusion: The mentioned factors may all be useful to identify PVC-iCMP patients who would benefit from RFCA, although the evidence is not yet strong enough.

Keywords: PVC-iCMP, catheter ablation, LVEF improvement, systematic review, prognosis, radiofrequency.

1. INTRODUCTION

Premature ventricular contraction (PVC) is a common arrhythmia with a high prevalence rate [1]. While isolated PVCs can be asymptomatic and cause no serious harm in an otherwise healthy heart, there is overwhelming evidence suggesting that frequent PVCs can result in reversible cardiomyopathy (CMP) characterized by left ventricular (LV) enlargement and impaired ejection fraction (EF) [2, 3]. There

has been a wide range of studies on PVC-induced cardiomyopathy (PVC-iCMP), exploring the risk factors for developing the condition, its management methods, and their efficacy. Radiofrequency catheter ablation (RFCA) of the PVC site of origin is an effective and popular treatment method to reduce frequently occurring PVCs and reverse the consequent CMP [4]. Previous studies have defined RFCA success as either reducing at least 80% of PVC burden (*i.e.*, the number of PVCs per day) or left ventricular ejection fraction (LVEF) normalization or improvement. Multiple factors such as PVC burden and its QRS duration, are associated with the progression of frequent PVCs into cardiomyopathies [5, 6]. However, there is a paucity of evidence on

*Address correspondence to this author at the Electrophysiology Department, Tehran Heart Center, Tehran University of Medical Sciences, Tehran, Iran; E-mail: avasheghani@tums.ac.ir

the predictors of LVEF improvement after RFCA treatment in patients with PVC-iCMP. As a result, we systematically reviewed the currently existing literature to determine these prognostic factors, based on a key question: “What variables can predict LVEF improvements after RFCA of the PVC site of origin in patients with PVC-iCMP?” We developed a framework of “population, intervention, outcome, and predictive factors” to better address our review question.

2. METHODS

2.1. Protocol and Registration

This systematic review follows the PRISMA method (Fig. 1). We developed and followed a review protocol (reg-

istered with the registration number “CRD42017078958” and fully available at http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017078958) in line with PRISMA-P 2015. Our full report describes the methods we used in detail.

2.2. Eligibility Criteria

We defined each of our review question components as presented in Table 1.

Because the predictive factors were not well-known prior to the review, we considered some that we had come across before the systematic search and the ones we theoretically believed to be important. We specifically sought studies with

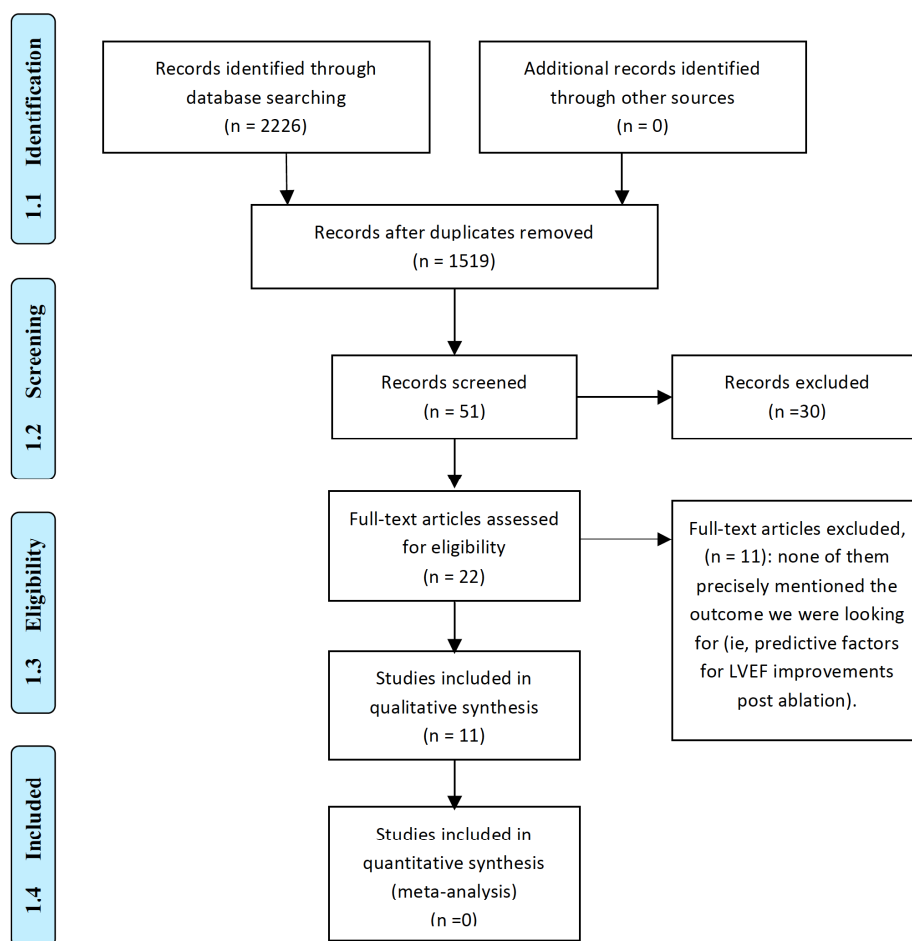


Fig. (1). PRISMA 2009 flow diagram. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

Table 1. Basic characteristics of the review question components.

Population	Intervention	Outcome	Prognostic Factors
Patients with PVC-induced cardiomyopathy (i.e., patients having reduced LVEFs) without any known underlying cause other than frequent PVCs (No cutoff for PVC burden was defined due to a lack of definition in the literature.)	Radiofrequency catheter ablation	Treatment success (LVEF improvement by at least 10%)	Duration of cardiomyopathy?/site of origin?/PVC burden? /PVC duration?/ PVC morphology ?/ age?/ sustained successful ablation?/ LVEDD?/ baseline LVEF?/ other possible factors?

Abbreviations: PVC, Premature ventricular contraction; LVEF, Left ventricular ejection fraction; LVEDD, Left ventricular end-diastolic volume.

an answer to our study question in any way, even if those studies were not initially planned to answer our study question, but had the desired results. Furthermore, although we initially considered LVEF improvements $>10\%$ to be the favored outcome in our review protocol, we also included LVEF improvements of $\geq 5\%$ (which are considered significant by a selected study) or $\geq 50\%$ after RFCA, in order not to miss any useful studies that had set these criteria for themselves.

2.3. Information Sources and Searches

Using a pre-defined search strategy (Appendix 1), we searched MEDLINE, Embase, Cochrane Library, Cochrane Collaboration, and Cochrane Database of Systematic Reviews (CDSR). All peer-reviewed publications in these databases were included with no date/language limitation until the end of 2017. Only studies in the full-text format were considered eligible since the evaluation of parameters such as the risk of bias was not completely feasible with the incomplete papers such as conference abstracts. We also searched the bibliographies of relevant articles so as not to miss any suitable data concerning our review question. At first, our search strategy contained 4 main keyword categories based on 1) population: patients with PVC-iCMP; 2) intervention: RFCA; 3) outcome: treatment success (LVEF improvements); and 4) predictive/prognostic factors. However, since the number of results produced by this search was not high enough, we reduced our keywords to only “population” and “intervention” to extend our results. Terms were extended to take into account spelling differences of keywords between American and British countries and journals in order not to miss any probable data.

2.4. Study Selection

After the evidence was gathered from the selected databases, it was all imported to Mendeley software and the duplicates were removed. Two reviewers (F.Z.T. and A.S.) independently screened the results using a 3-stage approach to reviewing the title, the abstract, and the full text. A third independent reviewer (MH. A.) was appointed to resolve any possible discrepancies in the article selection process, although it proved unnecessary after the screening as the results obtained by the first 2 authors matched. For studies to be selected, we set no limitations based on their language, type, or duration. Nevertheless, we only selected the ones with a sample size of at least 10 since we believed lower sample sizes could not have the required significance.

Regarding the risk of bias in individual studies, we included all good-quality studies that addressed our desired population, intervention, outcome, and predictive factors. In our final report, we also included relevant findings from good-quality studies that did not exactly address our review question but had some useful information that could assist in future studies.

2.5. Data Collection, Quality Assessment, and Summary Measures

One investigator (F.Z.T.) extracted the data regarding the design and methods of each study, their baseline population

characteristics, their predictive factors, and other relevant results from all the included studies and arranged the data in a standardized evidence table. Another investigator (A.V. F.) checked these data for accuracy. After identifying the type of each selected study, two investigators (A.M. and M.H.A.) independently assessed the quality of each study as “good,” “fair,” or “poor” by using the Joanna Briggs Institute (JBI) 2017 Critical Appraisal Checklist for the respective type of study [7]. We used this critical quality assessment tool because some of our included studies were quasi-experimental. Unlike critical appraisal skill program (CASP), JBI had a checklist specifically designed for these types of studies. We excluded all poor-quality studies, defined as studies having a fatal error or multiple important limitations based on the JBI checklist, confirmed by both investigators. The investigators resolved any disagreements through discussion.

3. RESULTS

Our initial search yielded 2226 titles; the number decreased to 1519 after removing the duplicates. After title screening of the remaining results, we selected 51 abstracts for a deeper review. We chose 22 of them for a full-text review. Finally, after consideration of the inclusion and exclusion criteria, we included 11 full-text articles in our systematic review (Table 1). None of these studies were poor-quality. Finally, we included 2 cohorts, 7 quasi-experimental studies, 1 case-control and 1 meta-analysis. Table 2 exhibits the type, methods, and results of each individual study. Table 3 demonstrates the quality of the included studies, as well as the level of evidence they produce.

4. DISCUSSION

4.1. Basic Considerations

Despite the lack of a well-defined nature, PVC-iCMP is commonly referred to as a condition in which there is a lower-than-normal LVEF ($<50\%$) or a higher-than-normal left ventricular end-diastolic diameter (LVEDD) in the presence of frequent PVCs while no other factors can be detected as the cause of CMP. Duffy *et al.* [18] initially depicted the concept (*i.e.*, frequent PVCs can cause LV dysfunction) in 1998, when they demonstrated that suppressing PVCs with antiarrhythmic drugs (AADs) was associated with LVEF improvements. Moreover, multiple studies since then have indicated that LV dimensions decrease after successful RFCA [2, 9, 19, 20]. However, subtle methods such as speckle-tracking imaging have revealed that PVCs are associated with LV dysfunction even in patients with preserved LVEFs [20]. Still, there is an ongoing debate concerning whether PVCs cause LV dysfunction (CMP) or result from an underlying CMP, the reason for which is unknown [12]. Accordingly, some studies have proposed terms such as “PVC-associated LV dysfunction” rather than PVC-induced LV dysfunction/CMP [4]. In addition, some studies have proposed an underlying occult structural heart disease (SHD) that cannot be detected by current imaging techniques as the cause of LV dysfunction in patients with frequent PVCs [21-23]. Nevertheless, we did not set strict criteria in this regard. Based on our search, virtually all the studies defined a successfully LVEF-improving RFCA as

Table 2. Results of the individual studies.

First Author, Year of Publication	Type of Study	Summary of Study Population and Methods	Predictive Factors	Statistical Reporting Method	SHD Evaluated/Addressed? (Methods/Explanations)	Relevant/Extra Findings/Conclusions
Baman, 2010 [8]	Quasi-experimental	174 patients with frequent idiopathic PVCs (33% with depressed LVEFs) underwent ablation; follow-up ≥ 1 year; Effective ablation was defined as $\geq 80\%$ reduction in PVC burden PVC-iCMP was defined as an improvement of an abnormal EF by at least 15% or normalized (EF $\geq 50\%$) post-ablation.	PVC burden	HR=1.12, 95% CI=1.08 to 1.16, and p<0.01	No (-)	PVC burden >24% was associated with PVC-iCMP.
Mountantonakis, 2011 [9]	Quasi-experimental	69 patients with nonischemic LVCM (age=51 \pm 16 y, LVEF=35 \pm 9%, and LVDD=5.8 \pm 0.7 cm); referred for ablation of frequent PVCs (burden=29 \pm 13%); follow-up=11 \pm 6 months; to assess the effect of residual PVCs and preexisting LVCM on the ablation outcome.	Ablation outcome (reducing PVC burden) Higher baseline LVEFs Absence of previous LVCM	HR=6.99, 95% CI= 3.99 to 9.92, and p<0.001 HR=1.51, 95% CI= 1.05 to 3.12, and p<0.001 HR=6.67, 95% CI=1.69 to 11.17, and p=0.011	No (-)	Decrease of at least 80% in PVC burden or to < 5000 residual PVCs per day predicted LVEF improvement regardless of the PVC site of origin. Lower LVEFs at baseline, even in the absence of preexisting LVCM, predicted less improvement after ablation, suggesting that cardiomyopathy may become irreversible if the treatment is delayed too long. It is possible that continued improvement would have been observed with a longer follow-up.
Deyell, 2012 [10]	Prospective Cohort	114 successfully ablated patients; pre-ablation PVC burden $\geq 10\%$; LVEF <50% (66 with normal LVEFs and 48 with impaired LVEFs); median follow-up=10.6 months; Patients were categorized into reversible ($\geq 10\%$ increase to a final LVEF $\geq 50\%$) or irreversible ($\leq 10\%$ increase or a final LVEF<50%) LV dysfunction groups.	PVC QRS duration	OR=5.07, 95% CI=1.22 to 21.01 per 10 ms increase, and p=0.003	No (-)	PVC QRS duration was also independently associated with baseline LV dysfunction. No single cutoff value could precisely discriminate reversible from irreversible LV dysfunction, but patients with a PVC QRS duration of ≥ 170 ms are unlikely to normalize their LV function, even after ablation.
Yokokawa, 2012 [11]	Quasi-experimental	264 patients with frequent idiopathic PVCs (87 with LV dysfunction [LVEF=40 \pm 10]); The aim: to determine the time course and predictors of LVEF recovery after ablation in PVC-iCMP patients.	Epicardial PVC origin	OR=11.1, 95% CI=1.42 to 86.8	Yes (All participants were evaluated for SHD with echocardiography, stress testing and/or CMR. Patients with SHD were excluded.)	Epicardial origin of PVCs was a predictor of delayed LVEF improvements post ablation. If the ablation is successful, PVC-iCMP is usually resolved within 4 months of ablation.

(Table 2) Contd...

First Author, Year of Publication	Type of Study	Summary of Study Population and Methods	Predictive Factors	Statistical Reporting Method	SHD Evaluated/Addressed? (Methods/Explanations)	Relevant/Extra Findings/Conclusions
Penela, 2013 [12]	Quasi-experimental	80 patients (27 with SHD) with frequent PVCs (burden=22 ± 13%) and LVEF<50% underwent RFCA; follow-up with echocardiography and 24-hour Holter ECG at 6 and 12 months post-ablation. Successfully sustained ablation was defined as the persistent elimination of at least 80% of the baseline PVCs with only the first ablation episode and after 12 months.	Baseline PVC burden Persistent ablation success	OR=1.12, 95% CI=1.06 to 1.18, and p<0.001 OR=3.82, 95% CI=1.09 to 13.32, and p=0.036	Yes (Most of the 27 patients with SHD had previously been diagnosed elsewhere, except for 2 of them who were diagnosed in the study with cardiac magnetic resonance (CMR) imaging. Results were reported regardless of previous SHD.)	Ablation of frequent PVCs can cause progressive neurohormonal, structural, and functional development in patients with LV dysfunction, even if their cardiomyopathy is not caused by their PVCs. A 13% baseline PVC burden had 100% sensitivity and 85% specificity to predict an absolute increase ≥5% in LVEF after successful ablation. All patients with abnormal LVEFs should be screened for frequent PVCs.
Zang, 2014 [4]	Meta-analysis	MEDLINE was searched for cohort studies of patients undergoing RFCA. End points were LVEF and LVEDD changes post ablation. The association between the site of origin of PVCs and LVEF improvements was assessed by meta-regression. In the end, 15 studies with a total of 712 patients were included.	-	-	Yes (Many evaluated studies included patients with SHD.)	The site of origin is NOT a predictor of post-ablation LVEF improvement. RFCA of frequent PVCs significantly improved LVEF and reversed LV dimensions. RFCA of frequent PVCs was more effective in patients with depressed baseline LVEFs than in the ones with normal LVEFs.
Park KM, 2015 [13]	Prospective Cohort	57 patients with frequent PVCs (>10% daily), LVEF<50% and without SHD underwent PVC suppression either with medical therapy (18) or RFCA (39). Successful suppression was defined as ≥80% reduction of 24-hour PVC burden. Patients were assigned to 2 groups: reversible CMP (LVEF≥50 and LVEF improvements by at least 10% post-suppression and irreversible CMP (LVEF≤45% pre-ablation and <50% ≥6 months after successful suppression; follow-up = at least 12 months.	LVEDD and PVC QRS duration	Among the patients undergoing RFCA (39 patients): Mean PVC QRS duration=157.4±10.5 ms in the reversible CMP group vs. mean PVC QRS duration= 171.9±17.2 ms (p<0.01). Also in general (regardless of treatment with RFCA or drugs), the PVC QRS duration was significantly associated with LVEDD (Y=0.64; p<0.01).	Yes (CMR and coronary angiography. SHD was an exclusion criterion in the study.)	After successful suppression of PVCs in patients with frequent PVCs and depressed LVEF, LVEDD can predict the reversibility of LVEF. LVEDD>66 mm predicted irreversible CMP with 50% sensitivity, 100% specificity, 100% positive predictive value, and 81% negative predictive value.
Blaye-Felice, 2016 [14]	Quasi-experimental	96 patients with suspected PVC-iCMP underwent RFCA and the parameters related to >10% increase in LVEF post-ablation were assessed after a mean follow-up of 24 ± 21 months. Successful ablation was defined as >80% decrease in PVC burden.	Age	OR=1.09, 95% CI= 1.03 to 1.18, and p<0.01 in multivariate analysis).	Yes (29 patients had previous SHD. SHD data were acquired only <i>via</i> patients' history.)	In addition to a higher age, a lower PVC QRS amplitude was MARGINALLY associated with the lack of reverse remodeling.

(Table 2) Contd...

First Author, Year of Publication	Type of Study	Summary of Study Population and Methods	Predictive Factors	Statistical Reporting Method	SHD Evaluated/Addressed? (Methods/Explanations)	Relevant/Extra Findings/Conclusions
Wojdyla-Hordyńska, 2017 [15]	Quasi-experimental	109 patients (65 with underlying SHD) with frequent PVCs (>10000/day) underwent RFCA; follow-up= 6 months Successful ablation was defined as an 80% reduction in PVC burden.	Baseline PVC burden (>20000 per day)	OR=3.53, 95% CI =1.15 to 10.75, and p=0.023	Yes (Echocardiography, CMR, cardiac catheterization, or stress testing).	Age, gender, presence of SHD, baseline LVEF, site of origin, and PVC QRS duration were NOT predictors of LVEF recovery after RFCA.
Penela, 2017 [16]	Quasi-experimental	81 patients with frequent PVCs and LV dysfunction who underwent successful RFCA were followed up for at least 1 year.	Baseline PVC burden PVC QRS duration> 130 ms	OR=1.24, 95% CI =1.09 to 1.4, and p=0.001 OR=0.94, 95% CI =0.89 to 0.99, and p=0.03	Yes (Patients with previously diagnosed SHD were excluded, ischemic heart disease was ruled out by coronary angiography or non-invasive stress test before the ablation).	The best cut-off value of baseline PVC burden for predicting echocardiographic response was 12%, with 98% sensitivity and 90% specificity. LVEDD>63 mm is a negative predictor of significant LVEF recovery. LVEDD is an unreliable clinical factor for patient selection because patients with high LVEDD tend to have other underlying conditions contributing to their cardiomyopathy. Also, LVEF of these patients increased after ablation as well, meaning they may still benefit from it.
Krishnan, 2017 [17]	Case-control	Patients with a PVC burden of ≥10% PVC/24 h and left ventricular ejection fraction (LVEF) of <50% who underwent successful ablation. Subjects were classified as having reversible (a final LVEF ≥50%) or irreversible (final LVEF <50%) LV dysfunction on a follow-up echocardiogram. A reference (control) group with ≥10% PVC but normal LV function was also identified.	Post-PVC blood pressure elevation Post-PVC pulse pressure change PVC QRS duration	OR=4.61, 95% CI=1.45 to 15.83, and p<0.001 OR=5.2, 95% CI= 2.3 to 18.6 per 5-mm Hg Increase, and p< 0.001 OR= 2.78, 95% CI= 1.63 to 10.94 per 10-ms increase, and p< 0.001	Yes (Voltage mapping was used to identify myocardial scars and fibrosis. Note that this method cannot rule out some types of SHD including dilated or hypertrophic cardiomyopathy)	-

Abbreviations: PVC, Premature ventricular contraction; PVC-iCMP, Premature ventricular contraction-induced cardiomyopathy; LVEF, Left ventricular ejection fraction; LVDD, Left ventricular diastolic volume; LVEDD, Left ventricular end-diastolic volume; RFCA, Radiofrequency catheter ablation; SHD, Structural heart disease.

Table 3. Quality assessment and level of evidence for each individual study.

First Author, Year of Publication	Quality Assessment	Level of Evidence
Baman, 2010 [8]	Good	2b
Mountantonakis, 2011 [9]	Good	2b
Deyell, 2012 [10]	Good	2b
Yokokawa, 2012 [11]	Good	2b
Penela, 2013 [12]	Good	2b
Zang, 2014 [4]	Good	2a
Park KM, 2015 [13]	Good	2b
Blaye-Felice, 2016 [14]	Good	2b
Wojdyla-Hordyńska, 2017 [15]	Good	2b
Penela, 2017 [16]	Good	2b
Krishnan, 2017 [17]	Good	3b

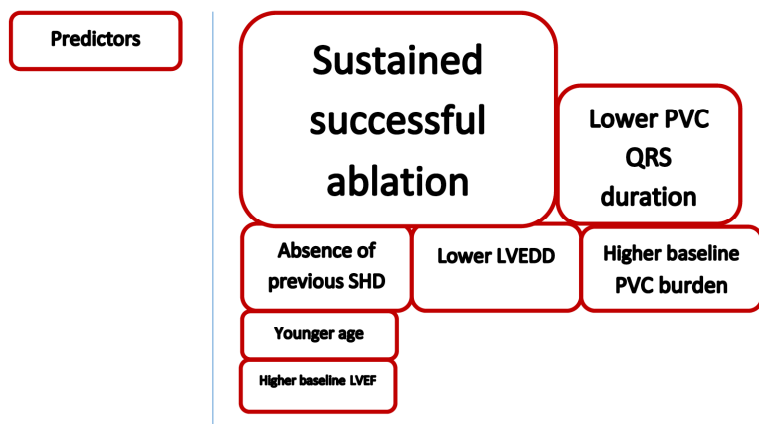


Fig. (2). Most important evidence-based predictors of LVEF improvement after RFCA of PVCs in order of level of significant evidence (bigger square size indicates stronger evidence). PVC, Premature ventricular contractions; RFCA, Radiofrequency catheter ablation; LVEDD, Left ventricular end-diastolic dimension; LVEF, Left ventricular ejection fraction; SHD, Structural heart disease. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

Table 4. A brief comparative demonstration of the results of different studies on some of the more frequently-reported predictive factors for LVEF improvement after successful RFCA.

Predictor	For	Against
Sustained Positive Ablation Outcome	Mountantonakis, 2011 [9] Yokokawa, 2012 [11] Penela, 2013 [12]	Penela, 2017 [16]
Higher Baseline PVC Burden	Penela, 2013 [12] Wojdyła-Hordyńska, 2017 [15] Penela, 2017 [16]	Deyell, 2012 [10] Park KM, 2015 [13] Krishnan, 2017 [17]
Lower PVC QRS Duration	Deyell, 2012[10] Park KM, 2015 [13] Krishnan, 2017 [17]	Yokokawa, 2012 [11] Wojdyła-Hordyńska, 2017 [15]
Younger Age	Blaye-Felice, 2016 [14]	Mountantonakis, 2011 [9] Wojdyła-Hordyńska, 2017 [15] Penela, 2017 [16]
Higher Baseline LVEF	Mountantonakis, 2011 [9]	Deyell, 2012[10] Park KM, 2015 [13] Wojdyła-Hordyńska, 2017 [15]

Abbreviations: LVEF, Left ventricular ejection fraction; RFCA, Radiofrequency catheter ablation; PVC, Premature ventricular contractions.

ablations resulting in LVEF improvements to $\geq 50\%$ or $>10-15\%$, although their follow-up periods were different. Zang *et al.*, and Mountantonakis, however, defined LVEF improvements $>5\%$ as clinically significant [4, 9]. Regarding a high PVC burden, there were various suggested ranges starting from $\geq 10\%$ to $29\pm 13\%$, reflecting the lack of a transparent cutoff for defining a high PVC burden. Moreover, even a burden of 4% was previously associated with CMP [24]. There are, however, studies suggesting that PVC burden $>24\%$ is a risk factor for PVC-iCMP, although 20-25% of the subjects in those studies did not have that burden [3, 8, 13, 25, 26]. The studies we selected were diverse with regard to their methodologies or even objectives. Nonetheless, we carefully extracted only the relevant results.

4.2. Main Findings

Regardless of all the differences in the selected studies, our review indicates that age, PVC burden, the ablation outcome, higher baseline LVEF, the PVC QRS duration, the absence of a previous CMP caused by factors other than frequent PVCs, successful sustained ablation, and the LVEDD are the suggested predictive factors for LVEF improvement after successful RFCA in patients with PVC-iCMP (Fig. 2). The epicardial origin of PVCs has also been previously suggested, but a meta-analysis on the effects of the PVC site of origin reported no predictive value for this factor [4]. Table 4 briefly compares the results of the studies on some of the more frequently-reported predictive factors.

4.3. Predictors of LVEF Improvement after Catheter Ablation

4.3.1. Sustained Successful Ablation

Successful ablation can reverse the CMP purely induced by PVCs and improve the LVEF. Most investigations define a successful ablation as $\geq 80\%$ reductions in PVC burden [8, 9, 12-15]. Mountantonakis *et al.*, also suggested < 5000 post-ablation residual PVCs as another indicator of ablation success [9]. However, there is no distinct definition of “sustained” success. Penela *et al.*, [12] considered 12 months of reduced PVCs as a sustained success. Nevertheless, there is no set criterion in this regard. Although long-term success rates for RFCA are high in the majority of studies, PVCs may reappear even after a successful ablation. According to a recent study by Baser *et al.* [27], the recurrence of PVCs after ablation resulted in the recurrence of PVC-iCMP. Furthermore, the study performed by Penela *et al.* [12] demonstrated that 93% of the recurrences occurred during the first 6 months after ablation. Given the unknown nature of the disease and the fact that many PVC-iCMP patients do not present any symptoms with regard to PVCs, it is safe to presume that all ablated patients need a scheduled short- and long-term follow-up to detect any recurring CMP at its initial phases.

4.3.2. Baseline PVC Burden

In the study performed by Baman *et al.* [8], the lowest baseline PVC burden that was associated with significant post-ablation LVEF improvement was 10%. Moreover, Penela *et al.* [12] reported no post-ablation LVEF improvements in subjects with baseline PVC burden $\leq 13\%$. Wojdyła-Hordyńska *et al.* [15] concluded that a cutoff of > 20000 PVCs per day was associated with better LVEF improvement. These findings suggest that the baseline PVC burden should exceed a certain value to develop a pure PVC-iCMP (which is also reversible). Lower PVC burden may indicate that the depressed LV function is probably due to an undetected, irreversible underlying cause rather than the PVCs alone. Nevertheless, because the significance of baseline PVC burden as a predictive factor for post-ablation recovery is questioned by some other studies (Table 4), further investigations on this variable seem necessary.

4.3.3. PVC QRS Duration

Conduction disturbances in the ventricles and the QRS duration are associated with the presence of any type of SHD in the general population [28]. Pathological studies on idiopathic LV cardiomyopathies have demonstrated myocardial remodeling that includes myofibrillar disarray and myocardial fibrosis [29, 30]. Hypothetically, the PVC QRS duration is thought to indicate the extent of this remodeling. Therefore, the irreversible underlying structural abnormality (*i.e.*, fibrosis) may account for the loss of LVEF improvements after ablating PVCs with higher QRS durations. Deyell *et al.*, did not suggest a cutoff but demonstrated that even the ablation of frequent PVCs could not improve the LVEF of subjects with PVC QRS durations of ≥ 170 ms [10]. Most recently, Penela *et al.*, [16] proposed a cutoff of > 130 ms. By contrast, some animal studies have revealed no long-term occurrence of fibrosis in PVC-iCMP [31]. Moreover, other studies such as those performed by Penela *et al.* [12] and Wojdyła-

Hordyńska *et al.* [15] argued that the PVC QRS duration was not independently associated with LVEF improvement. These findings call for further evaluations in the future. The sinus QRS duration could also be prolonged. However, the quick conduction through Hiss and Purkinje fibers may cover this subtle alteration in ECG.

4.3.4. Absence of a Previous SHD

The presence of an underlying structural heart abnormality could clearly alter the outcome in favor of failure as the ablation process may not affect this underlying condition. This is, however, argued by some studies such as the one by Wojdyła-Hordyńska [15], who demonstrated no correlation between the presence of SHD and LVEF improvement after ablation. Broader studies should be performed to discover the precise mechanisms through which SHD and PVCs affect each other and to identify the type of CMP in patients who experience both the conditions.

4.3.5. LVEDD

A study by Park *et al.* [13] revealed a “definitive positive linear correlation” between the PVC QRS duration and the LVEDD. They, therefore, used the link between higher QRS durations, irreversibility of CMP, and the LVEDD to suggest the LVEDD as an indicator of LVEF irreversibility post-ablation. They hypothesized that a long QRS duration indicates a delay in myocardial electrical conduction, which by itself could reflect LV dilation.

4.3.6. Age

As is demonstrated in a study by Blaye-Felice *et al.* [14], younger age is unsurprisingly a predictor of better LVEF improvement. Although no mechanism has been suggested, this is perhaps due to the irreversible structural changes in the heart that are induced by aging. It should be noted, however, that age was not associated with post-ablation LVEF improvement in the study by Wojdyła-Hordyńska *et al.* [15].

4.3.7. Baseline LVEF

It seems reasonable to assume that a lower pre-ablation LVEF is an indicator of poorer prognosis for LVEF improvement after ablation. Previous studies have linked lower baseline LVEF with less probability of LVEF improvement after some heart failure therapeutic methods such as cardiac resynchronization [32]. The findings of studies by Mountantonakis [9] and Penela [16] are in line with this theory. However, Wojdyła-Hordyńska *et al.*, [15] found no such correlation in their study. Lower baseline LVEF may indicate either an underlying CMP that is not caused only by frequent PVCs or that PVC-iCMP itself may progress into an irreversible form of CMP. Nevertheless, our knowledge on the matter is not much, and we need further evidence on this matter.

4.3.8. Post-PVC Systolic Blood Pressure Rise and Post-PVC Pulse Pressure Change

In the heart with no SHD, blood pressure increases after a PVC is followed by a sinus beat. This is most likely because of the inefficient heart contraction during a PVC, which leads to a prolonged diastolic filling time between pre- and post-PVC sinus beats. In a study, Krishnan *et al.* [17] found that the elevation of the systolic blood pressure after a PVC

as well as the subsequent alteration in post-PVC pulse pressure were directly associated with post-ablation LVEF recovery in patients with PVC-iCMP. They proposed that post-PVC systolic blood pressure elevation and post-PVC pulse pressure change could act as markers of cardiac contractility, suggesting that the disarray of cardiac fibers has not led to fibrosis and is reversible by ablation.

4.3.9. Epicardial Origin of PVCs

The ECG criteria that suggest an epicardial origin of PVCs are: 1) pseudo-delta wave, 2) maximal deflection index of >0.55 , or 3) the presence of the q wave in lead I [33]. Though Yokokawa *et al.*, [11] demonstrated that an epicardial PVC origin was associated with a “delayed” LVEF recovery post-ablation, they could not explain the reason behind this finding. Considering the fact that several other studies including a meta-analysis [4, 9, 15] have rejected a significant association between the PVC site of origin and LVEF improvement after ablation, one should interpret this result with caution.

4.4. A Deeper Look Into the Selected Studies

Baman *et al.*, [8] reported that a baseline PVC burden of $>24\%$ is “associated with” PVC-iCMP. What naturally comes to mind by this report is that the baseline PVC burden is a risk factor for the development of PVC-iCMP and that these studies only report a risk factor rather than a predictive factor for ablation success, as do many other studies, all of which we excluded. However, because these studies specifically defined PVC-iCMP as an LVEF normalization ($EF \geq 50\%$) or improvement by at least 15% after an effective ablation, it is safe to conclude that PVC burden is both a risk factor for the development of PVC-iCMP and a predictive factor for successful ablation. Zang *et al.* [4] only evaluated the site of origin of PVCs as a probable predictive factor for LVEF improvement and found no association. Their study also included many patients with normal baseline LVEFs. However, we decided to include this study as it ruled out the prognostic value of an important factor (site of origin), which was theoretically thought to contribute to LVEF improvement post-ablation. This fact was further emphasized in most of our individually selected studies. Deyell *et al.* [10] mentioned referral bias as an important limitation of their study. Although this type of bias existed in several other similar studies, they specifically stated that some of their findings were affected by the fact that their subjects had already been referred for ablation, which means their condition was probably more complicated and not responsive to medical therapy. They reported that factors such as PVC burden, sinus QRS duration, multiple sites of the PVC origin, the PVC coupling interval, baseline LVEF, and non-sustained ventricular tachycardia were not predictive for LVEF improvement post ablation. As presented in our review, some of these factors are indeed linked with post-ablation LVEF improvement by other studies. Penela *et al.* [12], as well as Wojdyla *et al.* [15], included patients with SHD in their studies. This is worth noticing because most studies in this field considered SHD to be an exclusion criterion and attempted to select subjects with pure PVC-iCMP. The presence of patients with SHD is also probably the reason why no more than two-thirds of the subjects achieved successfully sus-

tained ablation in the study by Penela *et al.* The study by Park *et al.*, [13] was not performed purely on patients who underwent RFCA and some patients received anti-arrhythmic drugs to control frequent PVCs. However, they assessed the final outcome among those who were treated with RFCA. Thus, we considered their report relevant to our review.

4.5. Other Studies

Some of the studies we found during our systematic search lacked some key components we were looking for, but had relevant findings that could guide future studies. For instance, Ling *et al.* [34] set PVC burden as the primary outcome to compare the efficacy of RFCA and AADs for treating right ventricular outflow tract-originated frequent PVCs (>6000). They reported that the QS morphology of PVCs in lead I was associated with better RFCA outcome compared with rsr'/rsR' and $qR/R/Rs$ PVC morphologies. Therefore, they suggested that the QRS morphology in lead I could be a predictor of ablation success. However, they did not consider CMP in their study and performed it on a population with a mean LVEF $>55\%$, therefore, the study was not relevant to our final report. Sheldon *et al.* [35] further emphasized on the role of PVC morphology in ablation outcome by demonstrating that monomorphic PVCs are associated with better ablation outcome. However, they set a cut-off of ≥ 156 non-predominant PVCs per day to differentiate successful and unsuccessful ablation and used it instead of LVEF improvement as a measure of success. Zhong *et al.* [36] treated 510 patients with frequent PVCs ($>1000/d$) either with AADs or with RFCA. They demonstrated that a PVC coupling interval < 450 ms, less impaired LV function, and RFCA (compared with AADs) were predictors of LVEF normalization. Their original manuscript, however, lacked data separating LVEF improvement of patients with pure PVC-iCMP who underwent RFCA from others. Also, not all the participants in their study had depressed baseline LVEFs. In a recent study, Bas *et al.* [37] interestingly observed that patients with PVC-iCMP had lower amounts of PVC variability during a 24-hour time period compared with those with frequent PVCs who had not developed CMP. They concluded that having more constant PVCs during the day was associated with the development of PVC-iCMP and assumed that the protective effect of periods of heart “rest” in between high PVC episodes in patients with high 24-hours PVC variability suggested an underlying mechanism that needed to be further studied. Unfortunately, they did not evaluate the effect of this variability on LVEF improvement after ablation. Nevertheless, PVC circadian variability seems promising and future studies on this factor with longer follow-up periods could be rewarding. Latchamsetti *et al.*, [38] retrospectively analyzed a large cohort of 1185 patients referred for ablation of frequent PVCs (mean PVC burden = $20 \pm 13\%$) and attempted to assess the predictors of procedural success (mean follow-up of 1.9 years) They reported a right ventricular outflow tract PVC origin as the only predictor of post-ablation success while mentioning an epicardial origin of PVCs as an indicator of treatment failure. Unfortunately, their study included a large portion of patients with normal LVEFs and they did not evaluate these factors for patients with CMP in particular. However, future assessments specifically de-

signed for patients with PVC-iCMP seem reasonable to clarify the role of these factors.

5. FUTURE PERSPECTIVES

Factors such as PVC burden, PVC QRS duration, PVC coupling interval, and interpolated PVCs are associated with the occurrence of PVC-iCMP. However, some of them may not specifically be associated with LVEF improvement after ablation. It seems logical to assume that many of these factors can also be predictors of LVEF improvement after RFCA because they are related to whatever that causes the PVC-iCMP in the first place. Still, RFCA may not affect all of them and thus we suggest that specific studies be performed to assess the predictive role of these factors in ablation. Furthermore, even in the case of the factors discussed in this review, because the current studies have controversial results in many cases, more extensive studies on the subject and gathering further evidence seem necessary. Other than the factors described in the results section of our review and the ones mentioned earlier, we also propose that factors such as LV dimensions, echo indices, and the duration of CMP might all predict LVEF improvement post-ablation and should, therefore, be used as tools for patient selection for RFCA. In addition, underlying ECG changes apart from PVCs themselves could be other possible predictors. For instance, we suggest that the role of coexisting ECG abnormalities such as atrial fibrillation, bundle branch blocks, and QRS fragmentation patterns be well investigated. These factors indicate an underlying conduction disturbance which might be associated with structural changes in the heart such as scar tissues. Logically, all these changes could potentially affect the reversibility of a PVC-iCMP. The PVC morphology might also be considered, but evidence suggests that multiple morphologies of PVCs are not suitable tools for patient selection [2, 39]. Future studies should aim for evaluating the currently proposed predictive factors as well as the ones suggested theoretically.

6. LIMITATIONS

Only a few studies with a high level of evidence and acceptable quality were able to answer our review question. This heterogeneity made a systematic study difficult and a meta-analysis impossible. Also, our study was susceptible to probable pitfalls because of the limitations and lack of some important data in the original articles. Finally, most of the included studies had small sample sizes, suggesting that future studies with larger populations are required to yield stronger evidence.

CONCLUSION

We conclude that sustained successful ablation; higher baseline PVC burden, LVEF, and QRS duration; higher post-PVC systolic blood pressure rise and post-PVC pulse pressure change; the absence of a previous CMP caused by factors other than frequent PVCs; younger age; and lower LVEDD may all predict LVEF improvement after RFCA in patients with PVC-iCMP. Our findings guide physicians based on the most recent publications with a high level of evidence to properly make a clinical decision on which patients may require RFCA and who would not benefit from it.

However, further evaluations are needed due to the high amount of heterogeneity among different studies. Moreover, our knowledge of PVC-iCMP as a distinct entity is limited and studies should be performed to reveal the true nature and mechanisms of this condition. We suggest that other factors such as LV dimensions, echo indices, and the duration of CMP could also predict the patients who would benefit from RFCA.

CONSENT FOR PUBLICATION

Not applicable.

STANDARD OF REPORTING

PRISMA guidelines and methodology were followed in this study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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