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Catheter ablation for papillary muscle arrhythmias: A systematic review

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[Correction added on 11th May 2022, after first online publication: CRUI funding statement has been added.]

Abstract

Background: Catheter ablation of papillary muscle ventricular arrhythmias (PM-VAs) has been associated with unsatisfactory results. Features that may affect acute and long-term procedural outcomes are not well established.

Objective: To systematically review the available data in the literature assessing efficacy and safety of PM-VAs catheter ablation.

Methods: An online search of PubMed, Cochrane Registry, Web of Science, Scopus and EMBASE libraries (from inception to March 1, 2021) was performed, in addition to manual screening. Twenty-one observational noncontrolled case-series were considered eligible for the systematic review, including 536 patients.

Results: Postero-medial PM harbored 60.8% of PM-VAs, while antero-lateral PM and right ventricular PMs 34.9% and 4.3% of cases, respectively. The mean acute success rate of the index ablation procedure was 88.1% (95% CI 82.8% to 91.9%, $p < .001$, I^2 0%). After a mean follow-up period of 15.5 ± 17.4 months, pooled long-term arrhythmia-free rate was 69.2%, while the pooled long-term success rate after multiple ablation procedure was 84.9%. Overall, procedure complications occurred in nine patients (1.7%) and no procedure-related deaths were reported. The use of intracardiac echocardiography (ICE) as well as contact force sensing (CFS) and irrigated catheters during ablation was associated with higher rates of arrhythmia-freedom at long-term follow-up.

Conclusions: Catheter ablation is an effective and safe strategy for PM-VAs, with an acute success rate of 88.1%, a long-term success rate of 69.2%, with a relatively low procedural complication rate. The use of ICE, irrigated catheters and catheters with CFS capability was associated with higher rates of arrhythmia-freedom at long-term follow-up.

KEYWORDS
intracardiac echocardiography, irrigated ablation catheters, papillary muscle, ventricular arrhythmias

1 | INTRODUCTION

Ventricular arrhythmias (VAs), such as premature ventricular contractions (PVCs) or ventricular tachycardia (VT), can originate from different structures inside the ventricles.[1] Papillary muscles (PMs) have become increasingly recognized as a possible site of origin of arrhythmias with typical electrocardiographic features (Figure 1), both in patients with and without structural heart disease (SHD), representing the site of origin of almost 5% of all idiopathic PVCs referred for ablation.[2] Catheter ablation is an effective and safe therapeutic strategy for VAs, with success rate as high as 93% for arrhythmias originating from right ventricular outflow tract (RVOT).[3] However, catheter ablation of PM-VAs has historically been associated with lower acute success rates (80%) and unsatisfactory long-term results (60% out of antiarrhythmic drugs), mainly due to the complex anatomy, the variable location of the ventricular arrhythmia site of origin and changing exits during ablation linked to anisotropic conduction.[3–5] During the past years, small studies have reported the outcomes of PM-VAs ablation using different catheter technologies, energy sources and preprocedural and intraprocedural imaging modalities. In this report, we aimed to systematically review the available data in the literature and assess the efficacy and periprocedural complication rates following catheter ablation for PM-VAs.

2 | METHODS

2.1 | Search strategy, selection criteria and outcomes

The present systematic review was performed according to Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta–Analyses (PRISMA) statements.[6] This study was approved by the Institutional Review Boards on Human Research.

An online search of PubMed, Cochrane Registry, Web of Science, Scopus and EMBASE libraries (from inception to March 1, 2021) was performed, in addition to manual screening. We used the following keywords: ([papillary muscle]) AND ([ablation] OR [catheter ablation] OR [cryoablation] OR [radiofrequency ablation]) AND ([VAs] OR [VT] OR [premature ventricular contraction] OR [PVC]). No language restriction was applied. Reviews, editorials, letters, meta-analysis, case reports, and abstracts were excluded.

The systematic review included studies on patients undergoing catheter ablation of papillary muscle arrhythmias. In the absence of a control group, a non-controlled observational analysis was performed. To be considered eligible, observational non-controlled case series required at least five patients. The efficacy outcomes were acute termination of PM arrhythmias and long-term freedom from PM arrhyth-

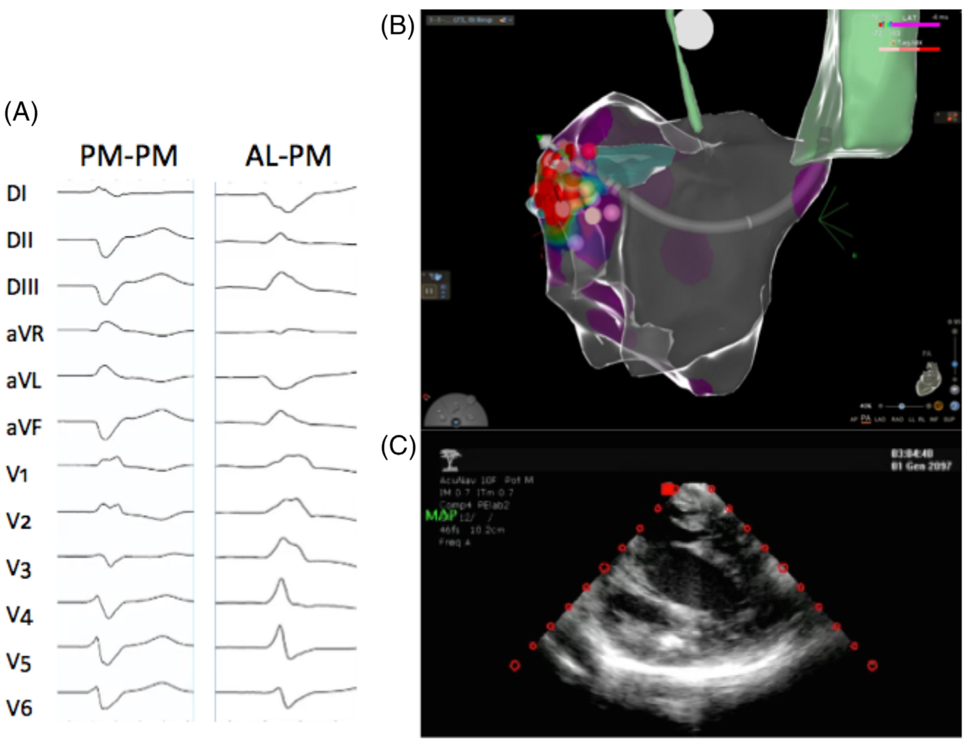


FIGURE 1 Electrocardiographic features of PM ventricular arrhythmias originating from posteromedial PM and anterolateral PM (panel A); posterior view of lesion set at the base and around the base of anterolateral PM (panel B); ICE imaging of anterolateral PM (panel C). AL-PM, anterolateral papillary muscle; PM-PM, posteromedial papillary muscle [Color figure can be viewed at wileyonlinelibrary.com]

mias after catheter ablation procedure. The safety outcomes included peri-operative mortality and procedure-related complications. Eligibility criteria required studies to provide patients' demographics and acute success rate of catheter ablation.

Two independent reviewers (M.V.M. and A.P.) screened all abstracts and titles to identify potentially eligible studies, of which full text was subsequently interrogated. Agreement of the two reviewers was required for eligibility of studies for analysis. Disagreements regarding the inclusion or the classification of a study were solved by a third reviewer (C.L.).

2.2 | Data extraction and quality assessment

Data extraction was performed by two reviewers (M.V.M. and A.P.). Where available, for each study the following data were collected: first author and year of publication, study design, number of patients, demographic data (age and sex), left ventricular ejection fraction (LVEF), presence of cardiomyopathy, site of origin of the arrhythmias (anterolateral PM, posteromedial PM or right ventricular PMs), procedural data (type of catheter, energy, procedural and fluoroscopy time), follow-up duration, acute and long-term success rates, procedural mortality and procedure-related complications.

Study quality was formally evaluated by two reviewers (M.V.M. and A.P.) using the National Heart, Lung, and Blood Institute Quality Assessment Tool for Case Series Studies.[7] The final classification of the studies required the agreement of both reviewers and any case of disagreement was solved by a third reviewer (C.L.).

2.3 | Statistical analysis

Descriptive statistics are presented as means and standard deviations (SD) for continuous variables normally distributed and median and 25/75 interquartile for continuous variables non-normally distributed, or number of cases (n) and as percentages (%) for dichotomous and categorical variables. Statistical analysis was performed using Comprehensive Meta-Analysis Software (Version 2), starting by events and simple size for each included study. The effect size assessed was prevalence of acute termination of PM arrhythmias and long-term freedom from PM arrhythmias after catheter ablation procedure. Overall prevalence and 95% confidence interval were estimated. Statistical heterogeneity on each outcome of interest was quantified using I^2 statistic. Values of I^2 statistic, ≤25%, 50%, and ≥75% indicated low, moderate, and high heterogeneity, respectively, whereas for Q statistic, substantial heterogeneity was defined as a $p < .1$. Data were pooled using a fixed-effect model, whereas a random-effect model was preferred if moderate heterogeneity among studies was found. In addition, we also performed subgroup analyses based on catheter technology used (contact force sensing [CFS] vs. no CFS, irrigated vs. non-irrigated catheters), the use of imaging to assist ablation (ICE vs. no-ICE), cardiomyopathy (idiopathic arrhythmias vs. arrhythmias in SHD).

3 | RESULTS

3.1 | Study selection and patient characteristics

As shown in Figure 2, among 237 papers, 27 studies met the inclusion criteria.[5,8–33] Subsequently, six studies were excluded because including duplicate patients.[5,8–12] Hence, 21 studies were included in final analysis (16 single center studies and five multicenter studies), with a total population of 536 patients undergone catheter ablation of PM arrhythmias[13–33] (Table 1). The mean age of the patients was 56.6 ± 16.3 years (female n = 191, 35.6%) and the mean LVEF was 47.8% ± 13.7%. Almost half of the patients (n = 244, 45.5%) presented cardiomyopathy at the time of ablation, whereas 6 studies included only patients with idiopathic arrhythmias, without SHD.[14,17–18,20,23,29] Cardiomyopathy was defined as any SHD, including ischemic heart disease (IHD), valvular heart disease (VHD) such as mitral valve prolapse (MVP) and dilated cardiomyopathy. The most common clinical arrhythmia was PVC, reported in 357 patients (67% of cases), while VT arising from PM was the only presenting arrhythmia in one study.[15] Nine studies (42.8%) reported the mean PVC burden before ablation with an overall burden of 21.1% ± 14.7%.[16,19–20,23,25,27–28,31,33] In the 12 studies reporting data on previous antiarrhythmic drug treatment, most patient undergone ablation after failure of at least one antiarrhythmic medication.[14–15,18–22,26–27,30–32] All the studies included in the analysis were observational case series, without control group. Six studies were prospective reports,[13–14,17,19–20,23] and 15 studies had a retrospective design.[15–16,18,21–22,24–33] Using the National Heart, Lung and Blood Institute Quality Assessment Tool for Case Series Studies,[7] 16 studies fulfilled eight criteria,[14,16,18–28,30,32–33] four studies fulfilled seven criteria,[13,15,17,31] and one study fulfilled six criteria.[29]

3.2 | Procedural data

PM arrhythmias were frequent or inducible during all the procedure. Overall, 554 PM were targeted, 355 posteromedial PM, 204 anterolateral PM and 25 right ventricular (RV) PM (4.3% of all PMVAs included). As shown in Table 2, 11 studies (52.3%) reported the procedure duration time (mean 212.7 ± 104.2 min)[16,18–20,25–27,29,31–33] and eight studies reported fluoroscopy time (mean 19.4 ± 17.8 min).[19–20,26–28,31–33] Intracardiac echocardiography (ICE) was used to guide mapping and ablation in 19 studies (86.4%).[14–23,25–33] In 13 studies ICE assisted all procedures,[15–16,19–23,25,28–31,33] whereas in six studies only a portion of the procedure was ICE-guided.[14,17–18,26–27,32] Three dimensional electroanatomical mapping system assisted the procedure in all cases (Biosense Webster CARTO system in 16 studies,[14,16–17,19–28,30–31,33] a combination of Biosense Webster CARTO system and Abbott-St. Jude

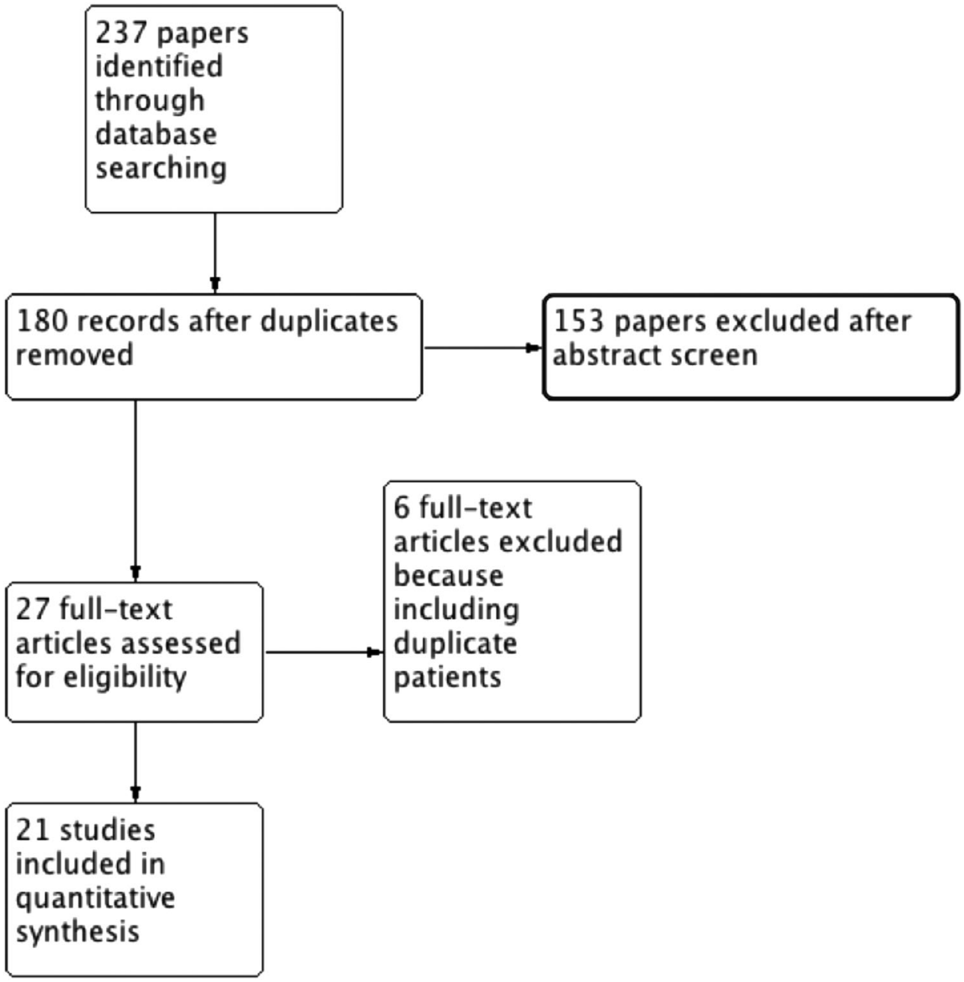


FIGURE 2 Study flow diagram

Ensite NavX in four studies,[15,18,29,32] a combination Biosense Webster CARTO system and Boston Scientific Rhythmia in one paper[13]). In four studies,[19–20,22,28] both robotic magnetic navigation-guided (RMN) ablation and manual ablation were used, combining the Stereotaxis Niobe ES magnetic navigation system (Stereotaxis, St. Louis, MO, USA) to CARTO mapping system. Access to the left ventricle was obtained through retrograde crossing the aortic valve in six studies[13–14,17–18,24,27] or trans-septal puncture in two studies.[19–20] In 10 studies both the approaches were used,[15,23,25–26,28–33] and in three studies the approach used for mapping and ablating the PM-VAs was not reported.[16,21–22] Mapping and ablation catheters features were reported in 95% of the studies (n = 20, Table 2). Irrigated catheters were used in 11 studies,[13,16,19–20,22–23,25–27,30–33] whereas in nine reports the procedure was performed using a combination of irrigated or nonirrigated.[14,17–18,21,24,28–29] A combination of catheters with and without CFS capabilities were used in seven studies,[26–28,30–33] whereas in 13 studies ablation was performed with catheters without CFS capabilities.[13–25] During activation mapping, the mean pre-QRS activation time was 29.6 ± 10.9 ms (Table 2). The discrete ablation site was reported in 38.1% of cases (eight studies,[13–14,18,20,25–26,32–33] 272 ablation procedures), and was mainly located at the base of the PM (115 cases, 42.3%), at PM tip (88 cases, 32.3%), at PM body (50 cases, 18.4%). In the last 19 ablation procedures (7%), the entire PM was targeted to successfully eliminate PM arrhythmias.[33] At successful ablation site, 15 studies (71.4%) reported the presence or absence of Purkinje-like potentials.[14,16–25,29–32] These potentials were recorded in 13 studies,[16–25,29,31–32] with a prevalence ranging from 22% to 67% and a total prevalence of 34.5% (108/313 procedures). A combination of radiofrequency and cryoenergy was used for ablation in three studies.[16,32–33] Radiofrequency application time was reported in 10 studies (47.6%),[16,18–21,25–26,29,31,33] with an overall mean radiofrequency time of 21 ± 19.1 min. For most of the studies, the acute ablation endopoint was the complete elimination and/or non-inducibility of PM arrhythmias with burst pacing or isoproterenol infusion.

3.3 | Procedural outcomes: efficacy and safety of catheter ablation

The mean acute success rate of the index ablation procedure was 88.1% (95% CI 82.8% to 91.9%, $p < .001$, I^2 0%) (Figure 3), with 10

TABLE 1 Baseline characteristics of the included studies

Study	Year	Centres	Design	Number of patients	Age (years)	Female (n;%)	Mean LVEF	Cardiomyopathy	PVC burden	Previous AADs failed	Quality
Doppalapudi et al.[13]	2008	Single center	Prospective	7	57.1 ± 15.1	2 (29%)	N.A.	2 (29%)	N.A.	N.A.	7
Yamada et al.[14]	2009	Single center	Prospective	6	62 ± 15	3 (50%)	60	0 (0%)	N.A.	Yes	8
Abouezzeddine et al.[15]	2010	Single center	Retrospective	5	69 ± 13.3	1 (20%)	41 ± 24	5 (100%)	N.A.	Yes	7
Yokokawa et al.[16]	2010	Single center	Retrospective	40	51 ± 14	25 (62.5%)	46 ± 13	20 (50%)	15.1 ± 12.9	N.A.	8
Yamada et al.[17]	2010	Single center	Prospective	19	59 ± 14	6 (32%)	63 ± 6	0 (0%)	N.A.	N.A.	7
Ban et al.[18]	2013	Single center	Retrospective	12	52 ± 9	7 (58%)	53 ± 9	0 (0%)	N.A.	Yes	8
Santoro et al.[19]	2014	Multicenter	Prospective	6	40 ± 11	4 (66.7%)	56.3 ± 9	1 (17%)	20.5 ± 9.3	Yes	8
Santoro et al.[20]	2014	Single center	Prospective	8	42 ± 13	6 (75%)	60 ± 4	0 (0%)	14 ± 3	Yes	8
Van Herendael et al.[21]	2014	Multicenter	Retrospective	8	56 ± 15	0 (0%)	N.A.	6 (75%)	N.A.	8 (100%)	8
Al'Aref et al.[22]	2015	Single center	Retrospective	18	68 ± 10	5 (28%)	N.A.	14 (78%)	N.A.	2 (11%)	8
Chang et al.[23]	2016	Single center	Prospective	13	40.2 ± 13.8	5 (38%)	58 ± 4	0 (0%)	11.6 ± 10.8	N.A.	8
Wo et al.[24]	2016	Single center	Retrospective	16	47 + 13	5 (31%)	59 ± 12	2 (12.5%)	N.A.	N.A.	8
Peichl et al.[25]	2017	Multicenter	Retrospective	34	62 ± 12	11 (32%)	50 ± 9	7 (21%)	22 ± 10	N.A.	8
Proietti et al.[26]	2017	Multicenter	Retrospective	16	67 + 6	5 (31%)	40.1 + 11	10 (63%)	N.A.	Yes	8
Lee et al.[27]	2018	Single center	Retrospective	23	52 ± 19.6	7 (30%)	47 ± 12	12 (52%)	25.3 ± 17.5	Yes	8
Bassil et al.[28]	2018	Single center	Retrospective	35	65 ± 12	11 (31%)	43 ± 13	12 (34)	16 ± 21	N.A.	8
Li et al.[29]	2018	Multicenter	Retrospective	21	41.8 ± 16.4	7 (34%)	N.A.	0 (0%)	N.A.	N.A.	6
Itoh et al.[30]	2018	Single center	Retrospective	34	56 ± 18	16 (47%)	N.A.	15 (44%)	N.A.	Yes	8
Enriquez et al.[31]	2019	Single center	Retrospective	25	54.7 ± 15.7	16 (64%)	50.5 ± 11.8	25 (100%)	24.4 ± 13.1	23 (92%)	7
Rivera et al.[32]	2019	Single center	Retrospective	53	49 ± 17	18 (34%)	53 ± 11	30 (57%)	N.A.	Yes	8
Lin et al.[33]	2020	Single center	Retrospective	137	62 ± 15	31 (23%)	42.0 ± 14.5	83 (61%)	24 ± 14	N.A.	8
Total				536	56.6 ± 16.3	191 (35.6%)	47.8 ± 13.7	244 (45.5%)	21.1 ± 14.7%		

Abbreviations: AADs: antiarrhythmic drugs; LVEF: left ventricular ejection fraction; N.A: not available; PVC: premature ventricular contraction.

TABLE 2 Procedural characteristics

Study	PM	Mapping system % (n)	ICE	Catheters	Energy source	CFS	RF or Cryo application time (min)	Procedural time (min)	Fluoroscopy time (min)	Approach	PLPs	Ablation site	Pre-QRS activation time (ms)
Doppalapudi et al.[13]	LVPM 7	Carto/Rhytmia	No	Irrigated	RF	No	N.A.	N.A.	N.A.	TA	N.A.	100% base	29 ± 2
Yamada et al.[14]	LVAL 6	Carto	Yes (66%)	Both	RF	No	N.A.	N.A.	N.A.	TA	0 (0)	3 base, 3 middle	27 ± 7
Abouezzeddine et al.[15]	LVPM 3, LVAL 2	Carto-NavX	Yes	N.A.	RF	No	N.A.	N.A.	N.A.	Both	N.A.	N.A.	N.A.
Yokokawa et al.[16]	LVPM 21, LVAL 13, RV 8	Carto	Yes	Irrigated	RF/Cryo*	No	24.5 ± 13.8	323.5 ± 100	N.A.	N.A.	15 (37.5%)	N.A.	30.3 ± 16.1
Yamada et al.[17]	LVPM 12, LVAL 7	Carto	Yes (68%)	Both	RF	No	N.A.	N.A.	N.A.	TA	8 (42%)	N.A.	27 ± 7.3
Ban et al.[18]	LVPM 10, LVAL 2	EnSite-NavX (17%)	Yes (42%)	Both	RF	No	16 ± 16	156 ± 86	N.A.	TA	4 (33%)	12 base	35 ± 11
Santoro et al.[19]	LVPM 2, RVPL 4	Carto/Stereotaxis	Yes	Irrigated	RF	No	19 ± 12	367 ± 141	57.3 ± 30	TS	4 (66.7%)	NA	42 ± 12
Santoro et al.[20]	RV septal PM 8	Carto/Stereotaxis 25%	Yes	Irrigated	RF	No	10.3 ± 3	76.3 ± 27.5	36.4 ±11.3	TS	2 (25%)	6 base, 1 middle and 1 tip	28.3 ± 4.8
Van Herendael et al.[21]	LVPM 6, LVAL 1,RV posterior PM 1	Carto	Yes	Both	RF	No	26 ± 15	N.A.	N.A.	N.A.	5 (63%)	N.A.	49 ± 15
Al'Aref et al.[22]	LVPM 9, LVAL 9	Carto/Stereotaxis	Yes	Irrigated	RF	No	N.A.	N.A.	N.A.	N.A.	4 (22%)	N.A.	23 ± 6
Chang et al.[23]	LVPM 8, LVAL 5	Carto	Yes	Irrigated	RF	No	N.A.	N.A.	N.A.	Both	4 (31%)	N.A.	37.2 ± 13.0
Wo et al.[24]	LVPM 8, LVAL 8	Carto	No	Both	RF	No	N.A	N.A.	N.A.	TA	7 (44%)	N.A.	38 ± 7
Peichl et al.[25]	LVPM 19, LVAL 12, both 3	Carto	Yes	Irrigated	RF	No	12.5 ± 8.7	162 ± 63	N.A.	TA 21, TS 10, both 3	10 (28%)	67% tip, 19% mid, 14% base	31 ± 9
Proietti et al.[26]	LVPM 21, LVAL 7	Carto	Yes (63%)	Irrigated	RF	Both	7.9 ± 3.6	213 ± 65	25 ± 15	15 TA, 9 TS	N.A.	13 base, 13 middle, 2 tip	35 ± 5
Lee et al.[27]	LVPM 11, LVAL 6, 6 both	Carto	Yes (83%)	Irrigated	RF	Both	N.A.	230 ± 62	17 ± 16.5	TA	N.A.	N.A.	22 ± 18

(Continues)

TABLE 2 (Continued)

Study	PM	Mapping system % (n)	ICE	Catheters	Energy source	CFS	RF or Cryo application time (min)	Procedural time (min)	Fluoroscopy time (min)	Approach	PLPs	Ablation site	Pre-QRS activation time (ms)
Bassil et al.[28]	LVPM 14, LVAL 20, RVPM 4	Carto/stereotaxis 69%	Yes	Both	RF	Both (11.4%)	N.A.	N.A.	12.2 ± 20.5	6 TA, 29 TS	N.A.	N.A.	27.7 ± 7.9
Li et al.[29]	LVPM 21	Carto-NavX	Yes	Both	RF	N.A.	13.8 ± 2.8	63.1 ± 16.2	N.A.	Both 5	6 (29%)	N.A.	27.2 ± 8.4
Itoh et al.[30]	LVPM 20, LVAL 8, both 6	Carto	Yes	Irrigated	RF	Yes	N.A.	N.A.	N.A.	Both	0 (0%)	N.A.	22 ± 8
Enriquez et al.[31]	LVPM 14, LVAL 8, 3 Both	Carto	Yes	Irrigated	RF	Both	35 ± 31	271 ± 81	34 ± 22	21 TA, 4 TS	7 (28%)	N.A.	30.6 ± 8.1
Rivera et al.[32]	LVPM 45, LVAL 8	Carto-EnSite	Yes (26%)	Irrigated	37 RF/16 Cryo	Yes (26%)	N.A.	144.4 ± 44.4	10.7 ± 5	Both	32 (60%)	Base 63%; body 25%; apex 12%	32 ± 8.1
Lin et al.[33]	LVPM 73, LVAL 51, both 13	Carto	Yes	Irrigated	RF/Cryo	Both (71%)	23 ± 21	235 ± 92	19 ± 15	Both	N.A.	41% tip, 10% body, 35% base, 14% entire LV PAP muscle	29 ± 9.6
Total	LVPM 355 - LVAL 204 - RVPM 25	100%	19/21	11 irri-gate/9 both	18 RF/3 RF + Cryo	13 no CFS/7 CFS	21 ± 19.1	212.7 ± 104.2	19.4 ± 17.8	6 TA, 2 TS, 10 both	13/15 (87%)	115 base, 50 body, 88 tip, 19 entire PM	29.6 ± 10.9

Abbreviations: CFS, contact force sensing; ICE, intracardiac echocardiography; LVAL, left ventricular antero-lateral; LVPM, left ventricular postero-medial; NA, not available; PLP, Purkinje-like potential; PM, papillary muscle; RF, radiofrequency; RVPM, right ventricular papillary muscle; TA, transaortic; TS, trans-septal.

Study name	Statistics for each study				Statistics for each study
	Event rate	Lower limit	Upper limit	Z-Value	p-Value
Doppalapudi et al. 2008	0,938	0,461	0,996	1,854	0,064
Yamada et al. 2009	0,929	0,423	0,996	1,748	0,081
Abouezzeddine et al.	0,917	0,378	0,995	1,623	0,105
Yokokawa et al. 2010	0,775	0,621	0,879	3,266	0,001
Yamada et al. 2010	0,947	0,706	0,993	2,813	0,005
Ban et al. 2013	0,962	0,597	0,998	2,232	0,026
Santoro et al. 2014	0,929	0,423	0,996	1,748	0,081
Santoro et al 2014	0,944	0,495	0,997	1,947	0,052
Van Herendael et al.	0,944	0,495	0,997	1,947	0,052
Al'Aref et al. 2015	0,833	0,591	0,945	2,545	0,011
Chang et al. 2016	0,964	0,616	0,998	2,289	0,022
Wo et al. 2016	0,971	0,664	0,998	2,436	0,015
Peichl et al. 2017	0,735	0,565	0,856	2,628	0,009
Proietti et al. 2017	0,938	0,665	0,991	2,622	0,009
Lee et al. 2018	0,739	0,528	0,878	2,193	0,028
Bassil et al. 2018	0,743	0,575	0,860	2,743	0,006
Li et al. 2018	0,952	0,729	0,993	2,924	0,003
Itoh et al. 2018	0,986	0,809	0,999	2,973	0,003
Enriquez et al. 2019	0,800	0,600	0,914	2,773	0,006
Rivera et al. 2019	0,925	0,816	0,971	4,818	0,000
Lin et al. 2020	0,949	0,897	0,975	7,530	0,000
	0,881	0,828	0,919	9,126	0,000

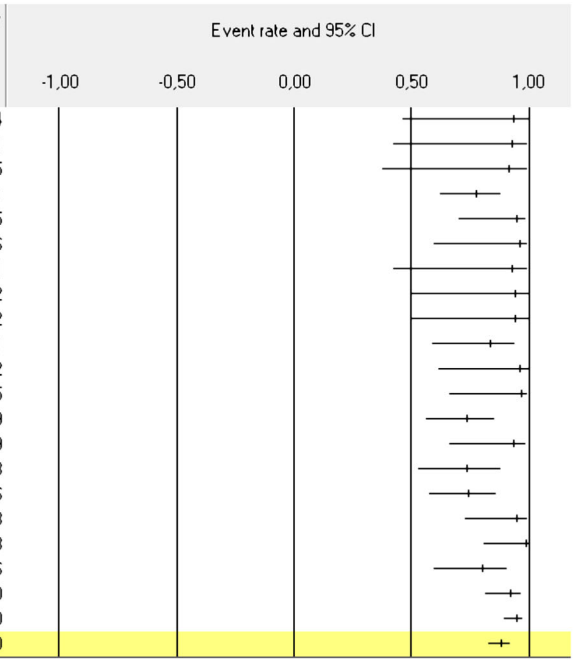


FIGURE 3 Acute procedural success [Color figure can be viewed at wileyonlinelibrary.com]

studies reporting an acute success of 100% (Table 3).[13–15,18–21,23–24,30] Data on long-term success after the index procedure, defined as absence of PM arrhythmia recurrences, were available for 14 studies.[13–14,17–19,21,23–26,29–30,32–33] During a mean follow-up period of 15.5 ± 17.4 months, 282 patients remained free from arrhythmia recurrences with pooled long-term arrhythmia-free rate of 69.2% (95% CI 60.5% to 76.6%, p < .001, I^2 23%) (Figure 4), while in 100 patients PM arrhythmias relapsed (Table 3). After the index procedure, 67 (12.5%) patients repeated procedures for recurrences and the long-term results after repeat ablation was available for eight studies. As shown in Figure 5, the pooled long-term success rate after multiple ablation procedure was 84.9% (95% CI 78.2% to 89.8%, p < .001, I^2 0%). Only 4 out 5 studies including RVPM arrhythmias reported the acute procedural outcome of catheter ablation, whereas the study by Bassil et al. did not report the acute success rate for RVPM VAs ablation.[16,19–21,28] Ablation was acutely successful in eliminating RVPM VAs in 100% of cases (21 patients), and only the study by Santoro et al.[19] reported the long-term success rate of RVPM VAs ablation (100%).

No procedure-related deaths were reported (Table 3). Eighteen studies reported absence of any procedural complications. Overall, procedure complications occurred in nine patients (1.7%). Lee et al.[27] reported one arteriovenous fistula in 23 patients (4.3%). Rivera et al.[32] described three complications related to PM arrhythmia ablation in 53 patients: one cardiac tamponade related to transeptal puncture and two minor complications (details not reported). Eventually, Lin et al.[33] reported an overall complication rate of 3.6% (n = 5) in 137 patients undergone PM ablation, including one acute aortic dissection related to cryo-catheter manipulation, two pericardial effusions requiring pericardiocentesis, one femoral pseudoaneurysm and one groin hematoma.

3.4 | Subgroup analyses

Acute success rate was lower in studies reporting ablation of PM arrhythmias related to cardiomyopathy (86.4%, 95% CI 79.7% to 91.1%, p < .001, I^2 0%) than in studies not including patients with cardiomyopathy (95.1%, 95% CI 87.6 to 98.1%, p < .001, I^2 0%). Similar pooled acute success rates were found when analyzing studies reporting all ICE-guided procedures versus studies reporting only a portion of ICE-guided procedures or not using ICE at all (86.9% vs. 90.1%, respectively), the use of irrigated and non-irrigated catheters (87% vs. 91.1% respectively) and the use of CFS and non-CFS catheters (87.6% vs. 83.8% respectively). Targeting arrhythmia exit sites was associated with numerically higher acute success rate (94.5%), although this approach was related to poorer outcome at long-term follow-up (72.3%). The use of an ICE-guided approach was related to numerically larger success rate at long-term follow-up compared to not using ICE (74.2%, 95% CI 65.5% to 81.3%, p < .001, I^2 0% vs. 61.2%, 95%CI 45.8% to 74.6%, p = .153, I^2 18%, respectively). At long-term follow-up, success rates were numerically lower when ablation was performed with nonirrigated versus irrigated catheters (58.7%, 95% CI 41.5% to 74%, p = .32, I^2 34% vs. 75%, 95% CI 68.8% to 80.3%, p < .001, I^2 0%), and when using non-CFS versus CFS catheters (66.4%, 95 CI 54.3% to 76.7%, p = .009, I^2 0% vs. 74.8%, 95% CI 61.4% to 84.7%, p = .001, I^2 0%). The results of subgroup analyses are shown in Table 4.

TABLE 3 Procedural outcomes

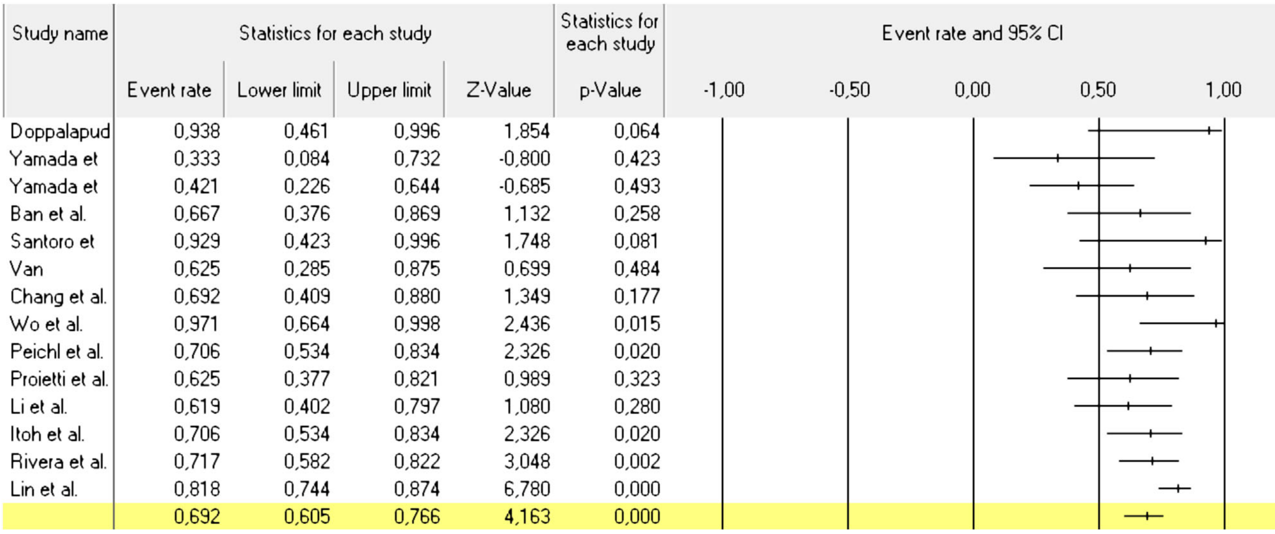
Study	Follow-up duration (months)	Acute success rate (%;N)	LT senza redo	Long-term success rate (%;N)	Procedural complications (%;N)	Procedural Mortality (%;N)	Redo Procedure
Doppalapudi et al.[13]	8.9 ± 5.3	100% (7)	100% (7)	100% (7)	0	0	0
Yamada et al.[14]	7 ± 4	100% (6)	33% (2)	67% (4)	0	0	2 (33%)
Abouezzeddine et al.[15]	N.A.	100% (5)	N.A.	N.A.	0	0	0
Yokokawa et al.[16]	32 ± 20	78% (31)	N.A.	N.A.	0	0	6 (15%)
Yamada et al.[17]	21 ± 12	95% (18)	42.1% (8)	89.5% (16)	0	0	9 (47%)
Ban et al.[18]	12±9	100% (12)	67% (8)	75% (9)	0	0	1 (8%)
Santoro et al.[19]	58 ± 11	100% (6)	100% (6)	100% (6)	0	0	0
Santoro et al.[20]	8 ± 4	100% (8)	N.A.	N.A.	0	0	0
Van Herendael et al.[21]	13.9 ± 24	100% (8)	62% (5)	62% (5)	0	0	0
Al'Aref et al.[22]	7.3 ± 26.8	83% (15)	N.A.	N.A.	0	0	N.A.
Chang et al.[23]	12.2 ± 6.9	100% (13)	69.2% (9)	92.3% (12)	0	0	3 (23%)
Wo et al.[24]	20 ± 12	100% (16)	100% (16)	100% (16)	0	0	0 (0%)
Peichl et al.[25]	13±16	74% (25)	71% (24)	NA	0	0	4 (12%)
Proietti et al.[26]	10.5 ± 7	96% (15)	62.5% (10)	87.5% (14)	0	0	7 (44%)
Lee et al.[27]	24	72% (17)	N.A.	N.A.	1 (4.3%) fistola AV	0	0
Bassil et al.[28]	2.7 ± 11.4	73.5% (26)	N.A.	N.A.	0	0	1
Li et al.[29]	5–70	95.2% (20)	60% (13)	90.5% (19)	0	0	8 (38%)
Itoh et al.[30]	16 ± 16	100% (34)	71% (24)	76% (26)	0	0	4 (11.7%)
Enriquez et al.[31]	31.5 ± 15.1	78% (20)	N.A.	N.A.	0	0	5 (20%)
Rivera et al.[32]	13.2 ± 12.3	92% (49)	72% (38)	N.A.	3 (5.6%), one cardiac tamponade related to transeptal puncture	0	0 (0%)
Lin et al.[33]	14.4 ± 15.9	95% (130)	82% (112)	91% (125)	5 (3.6 %), one acute aortic dissection, two pericardial effusions requiring pericardiocentesis, one femoral pseudoaneurysm, one groin hematoma	0	15 (11%)
Total	15.5 ± 17.4	88.1% (485)	69.2% (282)	84.9% (259)	9/536 (1.7%)	0 (0)	67 (12.5%)

Abbreviations: AV, arteriovenosus fistula; LT, long-term; N.A, not available.

4 | DISCUSSION

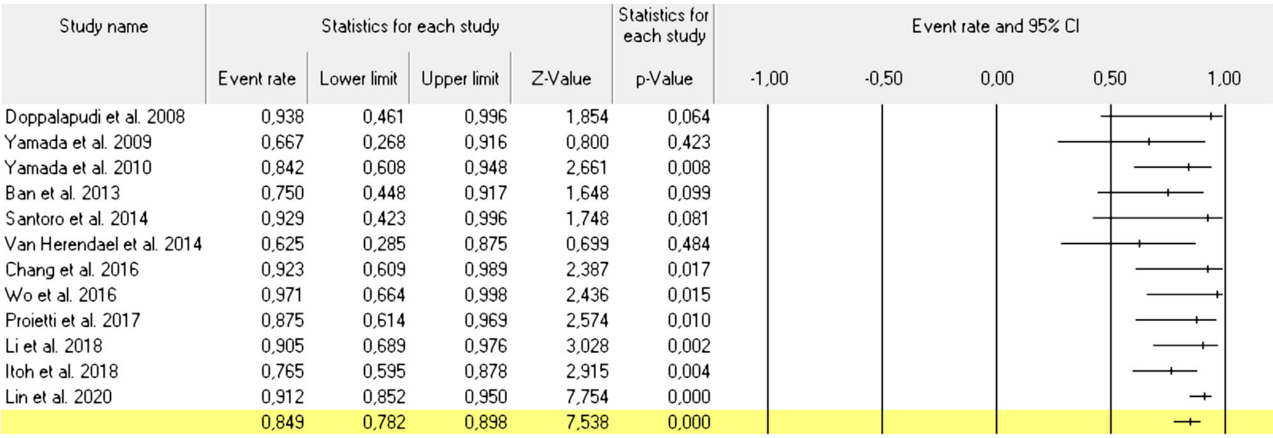
To our knowledge, this is the first systematic review on the ablation of PM-VAs. The major findings of this study are as follows: catheter ablation of PM-VAs is more effective and safe than previously thought, with high acute success rate that decreases at long-term follow-up; the presence of cardiomyopathy, including MVP, reduces the acute procedural success rate; the use of ICE-guided approach, as well as irrigated and CFS catheters are associated with higher rates of arrhythmia-free survival at long-term follow-up.

This systematic review shows that ablation of PM VAs has success rates as high as 88.1%, with low complication rate (1.7%). Generally, the outcomes related to the ablation of PM VAs, both in presence and absence of cardiomyopathy, have been poor, due to the complex anatomy, the variable location of the ventricular arrhythmia site of origin and changing exits during ablation linked to anisotropic conduction. In a retrospective multicenter analysis of the outcomes of idiopathic PVC ablation, acute procedural success was achieved in 80% of ablations, but PM arrhythmia origin was associated with the lowest long-term success rate (60%) when compared to RVOT, aortic cusps and epicardial arrhythmias.[3] Moreover, PM ablation was associated with the longest procedural time, the larger amounts of radiofrequency energy and high rate of repeat ablation procedures (36%). These findings have led to recommend catheter ablation for PM-VAs as second-line therapy, if antiarrhythmic medications failed, are not tolerated or not the patient's choice.[2] In line with previous studies, we report a long-term outcome of PM-VAs ablation after single procedure as high as 69.2%, and an overall freedom rate from PM-VAs after repeated abla-



Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value
Doppalapud	0,938	0,461	0,996	1,854	0,064
Yamada et	0,333	0,084	0,732	-0,800	0,423
Yamada et	0,421	0,226	0,644	-0,685	0,493
Ban et al.	0,667	0,376	0,869	1,132	0,258
Santoro et	0,929	0,423	0,996	1,748	0,081
Van	0,625	0,285	0,875	0,699	0,484
Chang et al.	0,692	0,409	0,880	1,349	0,177
Wo et al.	0,971	0,664	0,998	2,436	0,015
Peichl et al.	0,706	0,534	0,834	2,326	0,020
Proietti et al.	0,625	0,377	0,821	0,989	0,323
Li et al.	0,619	0,402	0,797	1,080	0,280
Itoh et al.	0,706	0,534	0,834	2,326	0,020
Rivera et al.	0,717	0,582	0,822	3,048	0,002
Lin et al.	0,818	0,744	0,874	6,780	0,000
	0,692	0,605	0,766	4,163	0,000

FIGURE 4 Long-term procedural success [Color figure can be viewed at wileyonlinelibrary.com]



Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value
Doppalapudi et al. 2008	0,938	0,461	0,996	1,854	0,064
Yamada et al. 2009	0,667	0,268	0,916	0,800	0,423
Yamada et al. 2010	0,842	0,608	0,948	2,661	0,008
Ban et al. 2013	0,750	0,448	0,917	1,648	0,099
Santoro et al. 2014	0,929	0,423	0,996	1,748	0,081
Van Herendael et al. 2014	0,625	0,285	0,875	0,699	0,484
Chang et al. 2016	0,923	0,609	0,989	2,387	0,017
Wo et al. 2016	0,971	0,664	0,998	2,436	0,015
Proietti et al. 2017	0,875	0,614	0,969	2,574	0,010
Li et al. 2018	0,905	0,689	0,976	3,028	0,002
Itoh et al. 2018	0,765	0,595	0,878	2,915	0,004
Lin et al. 2020	0,912	0,852	0,950	7,754	0,000
	0,849	0,782	0,898	7,538	0,000

FIGURE 5 Long-term success after repeated ablation procedure [Color figure can be viewed at wileyonlinelibrary.com]

tion of 84.9%. However, our analyses suggest that some procedural and patient characteristics may be associated with better acute and/or long-term outcomes. Although PM-VAs are often idiopathic, the presence of cardiomyopathy has been associated with PM arrhythmogenicity; in particular, recent reports have shown that mitral valve prolapse (MVP) is associated with PM-VAs in more than 25% of patients undergoing ablation.[27,31] In the absence of SHD, PM-VAs have a focal origin due to triggered activity or abnormal automaticity, whereas more complex reentrant arrhythmias are common in the presence of scar tissue. Acute success rate for catheter ablation of PM-VAs is lower in patients with cardiomyopathy (86.4%) than without SHD (95.1%), probably reflecting a more complex arrhythmic substrate.

Defining the anatomy and maintaining consistent catheter contact and stability during radiofrequency catheter deliveries are pivotal to suppress arrhythmogenic focus and definitely eliminate PM-VAs. However, PMs are thick and highly contractile intracavitary structures, with multiple surfaces, and the creation of durable lesions of adequate size and deepness is challenging, addressing the high rate of recurrences at long-term follow-up. Proietti et al[26] showed that the use of a three-dimensional ICE-guided electroanatomical approach was associated with higher long-term success rate when compared to an approach without ICE. More recently Lin et al.[33] reported an acute procedural success as high as 95% with ICE-guided catheter ablation, suggesting ablation as first-line therapy in the management of PM-VAs. In the current analysis the use of ICE to assist catheter stability, position and contact during ablation was related to similar acute procedural success (86.9%) as compared to not using ICE (90.1%), but long-term procedural success was better when ICE was used to assist ablation during the index procedure (74.2%) rather than ICE was not used (61.2%). Hence, in line with current guidelines on the management of VAs,[2] our analysis suggest that ICE may be preferred to assist ablation in order to increase procedural outcomes.

Lesion size during RF catheter ablation is directly related to the contact of ablating electrode with the tissue. Theoretically, CFS

TABLE 4 Subgroups analyses

	Acute success rate	Long-term success rate
Presence of cardiomyopathy	86.4%, 95% CI 79.7%–91.1%, $p < .001$, I2 0%	N.A.
Absence of cardiomyopathy	95.1%, 95% CI 87.6-98.1%, $p < .001$, I2 0%	N.A.
All ICE-guided procedure	86.9%, 95% CI 79.3%–92%, $p < .001$, I2 0%	74.2%, 95% CI 65.5%–81.3%, $p < .001$, I2 0%
Not all ICE-guided procedure	90.1%, 95% CI 82.2%–94.7%, $p < .001$, I2 0%	61.2%, 95%CI 45.8%–74.6%, $p = .153$, I2 18%
Irrigated ablation catheter	87%, 95% CI 80.3%–91.7%, $p < .001$, I2 0%	75%, 95% CI 68.8%–80.3%, $p < .001$, I2 0%
Non-irrigated ablation catheter	91.1%, 95% CI 79.8%–96.4%, $p < .001$, I2 0%	58.7%, 95% CI 41.5%–74%, $p = .32$, I2 34%
CFS ablation catheter	87.6%, 95% CI 76.3%–93.9%, $p < .001$, I2 0%	74.8%, 95% CI 61.4%–84.7%, $p = .001$, I2 0%
Non-CFS ablation catheter	83.8%, 95% CI 77%–89%, $p < .001$, I2 0%	66.4%, 95 CI 54.3%–76.7%, $p = .009$, I2 0%

Abbreviations: CI, confidence interval; CFS, contact force sensing; ICE, intracardiac echocardiography; NA, non available.

catheters may ensure lesion creation likely resulting in unexcitable areas. However, contrasting results on the effectiveness of CFS capability catheters for PM-VAs ablation have been reported. On the one hand, Rivera et al.[32] reported that an approach based on the use of non-CFS catheters and cardiac computed tomography integration (CTII) into the electroanatomical mapping system was associated with an increase risk of recurrence of clinical arrhythmia at long-term follow-up as compared to ICE-guided ablation performed with CFS catheters (48% vs. 7%). On the other hand, Lin et al.[33] did not find any difference between CFS group and non-CFS group neither in acute success (94% vs. 95%, $p = .79$) nor in clinical success during follow-up (84% vs. 78%, $p = .41$). Pooling data from different observational studies, our analysis showed that the use of catheters with CFS capability was related to higher percentages of freedom from arrhythmia recurrence (74.8%) as compared to non-CFS catheters (66.4%).

Nowadays, irrigated catheters are used worldwide because catheter irrigation allows greater power deliveries and creation of larger lesions by reducing tip-tissue interface temperature and charring formation. This aspect is crucial when approaching to PM-VA ablation because of the thickness of PMs and the frequent location of the focus deep inside the myocardium of PM base. Yamada et al[17] reported that the use of 4-tip non-irrigated catheters was associated with 100% rate of recurrence during long-term follow-up, and Yokokawa et al[16] found that failed ablation procedures were more common in patients with larger PMs mass, likely with an arrhythmogenic focus located away from the endocardial surface and hardly reachable regardless the use of irrigated catheters. Our analysis suggests that, although the acute success seems not to be affected by catheter irrigation status, long-term arrhythmia-free survival is numerically higher when using an irrigated catheter (75%) rather than a non-irrigated catheter (58.7%).

In consideration of the poor ablation outcomes obtained by targeting the earliest activation site, some Authors proposed an ablation strategy based on global pace-mapping of preferential conduction exits and/or the ablation all around the PMs eliminating all the endocardial exits near the PM base, thus isolating the arrhythmogenic focus.[23–24,30,32] In our analysis, this approach was associated with an acute success rate of 94.5%, but the success rate decreased at 72.4% at long-term follow-up. The large decrease in long-term as compared to the acute procedural results of this approach may be related to inadequate size and deepness of RF lesions, or to the presence of anatomical connections among PM body and left ventricular wall, relatively far from PM base. Indeed, Rivera et al.[34] recently described prevalence and clinical significance of PM connections (PMCs), detected at cardiac magnetic resonance (CMR) in patients undergone PM ablation. The prevalence of PMCs among patients experiencing arrhythmia recurrences was as high as 91%, suggesting that preferential conduction through either the PM base or PMCs may exist and may contribute to recurrences at follow-up. This finding underlines the need of anatomy understanding focusing RF deliveries in discrete zones potentially responsible of arrhythmia recurrences at long-term follow-up.

Maintaining catheter contact and stability is challenging during RF deliveries. To overcome this issue, current guidelines on catheter ablation of VAs suggest the use of cryoablation to achieve stabile contact during energy deliveries and improve procedure outcomes. Unfortunately, formal efficacy comparison between radiofrequency energy and cryoenergy has never been performed for PM-VAs so far. Yokokawa et al[16] reported the use of cryoablation for two PM-VAs and of RF energy for 40 PM-VAs, without reporting the outcomes for the different energy sources. Rivera et al[32] reported similar acute and long-term success rates when using cryoablation guided by CTII and ICE-guided CFS RF ablation, although 100% of patients undergone cryoablation achieved catheter stability versus 50% of patients undergone CFS RF energy ablation. Moreover, the use of cryo-catheter was not associated with proarrhythmic effects, whereas 78% of patients treated with RF energy developed catheter-induced arrhythmias (regardless CFS capability), further reducing catheter contact during RF energy delivery. Finally, Gordon et al[12] published a case series of 16 patients with failed RF ablation of PM-VAs in whom ablation strategy was intraprocedurally switched to cryoablation. Acute and long-term success rates were 93.8% (15/16), whereas in one patient the procedure was precluded by the development of acute aortic dissection while advancing the cryo-catheter in a retroaortic fashion to access the left ventricle. Overall, cryo-ablation seems an effective strategy to overcome stability and contact issues frequently encountered during RF ablation. However, some limitations of cryo-ablation should be mentioned: cryo-catheter may be more difficult to manipulate as compared to RF catheters due to its unidirectional steering ability and stiffness that may expose to aortic complications when advancing in a retroaortic fashion without the use of a long sheath. Hence, the decision to use cryo-ablation should be guided by local expertise and physicians' preference.

Evidence on RVPM VA ablation is scare in literature. In our report, RVPM VAs represented only 4.3% of all PM VAs included in the analysis (25 out 584). Five studies reported the outcome of RVPM VAs ablation, and among them 1 out 5 specifically included patients suffering from RVPM VAs.[16,19–21,28] The acute procedural success of RVPM VAs ablation was 100%, whereas only one study reported the long-term outcome of RVPM VAs ablation. Due to the paucity of data, any specific analysis on RVPM VAs ablation is impossible and no formal comparison with LVPM VAs could be carried out. Available, limited data suggested that the ablation of RVPM VAs, due to the different thickness, mobility and anatomical complexity of RVPM, may be less challenging as compared to LVPM VAs.[16,19–21,28] New evidences are awaited to shed light on the peculiarity and outcomes of RVPM VAs ablation.

4.1 | Study limitations

Although this is the first systematic review on PM-VAs ablation so far, several limitations should be considered. First, the included studies have an observational case series design, mainly retrospective, single-center and based on small cohorts. Due to the case series design of the available studies, an analysis event versus nonevents was not possible, thus hampering the strength of the study. Drawing solid conclusions from our analysis is impossible in the absence of comparative data on outcomes using different ablation strategies and technologies. Moreover, the majority of the included studies describe the results and the experiences of tertiary referral EP centers, possibly leading to an overestimation of acute and long-term success rates of the PM-VAs catheter ablation. However, we included in the analysis the best evidence available on the topic in literature, because no case-control or randomized controlled studies have been performed on PM-VAs ablation so far. Therefore, although limited, our study may provide some insights and foster large randomized controlled trial on the field. Second, antiarrhythmic therapy was not reported in all studies. Hence, the efficacy of catheter ablation may be overestimated if antiarrhythmic therapy after the procedure was used but not reported. Third, data regarding fluoroscopy time, procedure duration and presence of Purkinje-like potentials at the site of successful ablation are missing in several studies, precluding the analysis of the impact of catheters technologies on fluoroscopy time and procedure duration or of the association of Purkinje-like potentials with location of arrhythmogenic focus. Fourth, frequent PVC is associated with the development of PVC-induced cardiomyopathy.[35] The inclusion of PVC-induced cardiomyopathy among SHD was not homogeneous across the studies, thus possibly leading to an erroneous estimation of cardiomyopathy prevalence across the study population.

5 | CONCLUSIONS

Catheter ablation is an effective and safe strategy for PM-VAs, with an acute success rate of 88.1%, a long-term success rate of 69.2%, with a relatively low procedural complication rate of 1.7%. Data derived from low quality observational case-series studies show that the use of ICE, irrigated catheters and catheters with CFS capability are associated with higher rates of long-term procedural success of PM-VAs ablation.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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