

## Role of Cardiac Magnetic Resonance in the Assessment of Patients with Premature Ventricular Contractions: A Narrative Review

### ABSTRACT

Premature ventricular contractions (PVCs) are a common finding in clinical practice, requiring a full diagnostic work-up in order to exclude an underlying cardiomyopathy. Still, in a substantial proportion of patients, these investigations do not identify any substrate, and the PVCs are labelled as idiopathic. Cardiac magnetic resonance (CMR) has proven in the last decades as the method of choice for the exploration of patients with cardiomyopathies, since it can identify subtle changes in the myocardial tissue and help with risk stratification. In patients with idiopathic PVCs and a high PVC burden, several studies report the presence of late gadolinium enhancement (LGE) at CMR, which can offer additional diagnostic and prognostic benefits, as well as assistance in catheter ablation procedures, as the risk for adverse cardiac and risk for arrhythmic events events is higher compared to patients without scar. This paper focuses on the impact of the presence of LGE in patients with idiopathic PVCs, reviewing all the relevant studies published so far, including randomized controlled clinical trials, prospective or retrospective cohort studies, case series and case reports as well as systematic reviews.

**Keywords:** Premature ventricular contractions, cardiac magnetic resonance, late gadolinium enhancement, risk stratification

### INTRODUCTION

Premature ventricular contractions (PVCs) are common in patients undergoing long-term cardiological monitoring, accounting for approximately 90% of all ventricular arrhythmias (VAs). They are favored by older age, taller individuals, male sex, and other modifiable factors such as smoking, increased body mass index (BMI), sedentarism, and the use of excitants. Idiopathic PVCs develop in patients without underlying structural cardiac disease or metabolic imbalances thus, no specific treatment is recommended; nevertheless, patients with recurrent PVCs despite antiarrhythmic treatment may represent a challenge for the clinicians and may be referred for catheter ablation.<sup>1-4</sup>

Greater access to advanced cardiac imaging techniques, like late gadolinium enhancement cardiac magnetic resonance (LGE-CMR), has demonstrated in recent years that in patients who have idiopathic PVCs with a high PVC burden, myocardial scarring is often described by LGE-CMR. Cardiac magnetic resonance imaging is of great importance as it defines with great accuracy the left and right ventricular function and characterizes myocardial tissue by detecting focal fatty infiltration, tissue edema, and areas of necrosis or fibrosis that may be related to early-stage cardiomyopathies which otherwise would not be identified by conventional screening.<sup>5-7</sup>

Sudden cardiac death (SCD) has been associated with intramural scarring in patients without known coronary artery disease or acute myocardial infarction, regardless of the ejection fraction (EF). This finding supports the idea that the presence of nonischemic scarring may represent a risk factor for developing future arrhythmias and explains the quest for an active search of myocardial scarring in patients who present with idiopathic PVCs.<sup>8</sup>

### REVIEW

Stefan Ailoeai<sup>1,2</sup> 

Laurentiu Sorodoc<sup>2,3</sup> 

Carina Ureche<sup>1,2</sup> 

Gabriel Sandu<sup>1</sup> 

Nicolae Sitar<sup>1</sup> 

Alexandr Ceasovschi<sup>2,3</sup> 

Mihaela Grecu<sup>1</sup> 

Radu-Andy Sascău<sup>1,2</sup> 

Cristian Stătescu<sup>1,2</sup> 

<sup>1</sup>Department of Cardiology, Institute for Cardiovascular Diseases, Iași, Romania

<sup>2</sup>University of Medicine and Pharmacy, Iași, Romania

<sup>3</sup>Internal Medicine Clinic, Emergency Clinical County Hospital, Iași, Romania

#### Corresponding author:

Carina Ureche  
✉ carina.ureche@yahoo.com

Received: February 7, 2024

Accepted: May 7, 2024

Available Online Date: June 3, 2024

**Cite this article as:** Ailoeai S, Sorodoc L, Ureche C, et al. Role of cardiac magnetic resonance in the assessment of patients with premature ventricular contractions: A narrative review. *Anatol J Cardiol*. 2024;28(10):467-478.



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DOI:10.14744/AnatolJCardiol.2024.4314

This review focuses on the correlation between the presence, localization, and burden of PVCs, and myocardial scarring detected by LGE-CMR. Furthermore, we discuss the prognostic impact of this finding, in terms of SCD and other major cardiovascular outcomes such as VAs.

### Mechanisms of Premature Ventricular Contractions

There are 3 primary mechanisms which explain the occurrence of PVCs: triggered activity, enhanced automaticity and re-entry. First of all, triggered activity arises from an elevation in intracellular calcium levels, causing delayed after-depolarizations or abnormal cardiomyocyte depolarization following the depolarization phase (caffeine or digitalis toxicity). Enhanced automaticity occurs when specific myocardial tissues exhibit an intensified or exaggerated spontaneous generation of electrical impulses within the heart (myocardial ischemia, electrolyte imbalance, and increased adrenergic state). However, re-entry is a distinct mechanism requiring 2 electrical pathways with differential conduction. This mechanism is specific for regions affected by scar tissue and fibrosis, and represents the electrical substrate for monomorphic ventricular tachycardias (VT).<sup>9-11</sup> PVCs may originate in all structures of the heart, but the most prevalent PVC location in the general population is still up for debate. Common sites of origin include the right ventricle outflow tract (RVOT), the left ventricle outflow tract (LVOT), as well as the papillary muscles, mitral and tricuspid annulus, left ventricle (LV) summit, and the cardiac crux (Figure 1).<sup>3,10</sup>

### Clinical Studies Evaluating Premature Ventricular Contractions

Initial data regarding the prognostic impact of PVCs supported the idea that PVCs in individuals without structural heart disease do not influence their prognosis. In this regard, in a study conducted in 1985 by Kennedy et al<sup>12</sup> a group of 73 asymptomatic healthy participants was closely observed. These individuals were found to have frequent and complex PVCs, which were monitored using 24-hour Holter-ECG monitoring. The asymptomatic healthy status of the participants was confirmed through extensive non-invasive cardiac examinations. However, further investigations through cardiac catheterization in a subset of participants revealed that 19% of them had significant coronary artery disease. Nevertheless, it was concluded that the long-term prognosis for asymptomatic healthy individuals with frequent and complex PVCs is comparable to that of the general healthy population in the United States, indicating no elevated risk of mortality, since using the calculation of a standardized

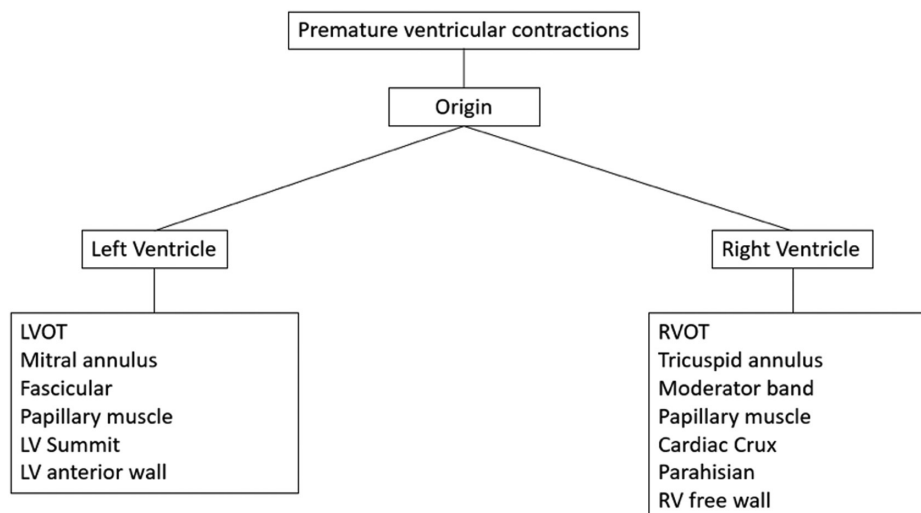
mortality ratio, 7.4 deaths were predicted but only 2 occurred (1 SCD and 1 from cancer).<sup>12</sup>

In the 90s and 2000s, it was postulated that frequent PVCs could potentially contribute to the development of heart failure in individuals with LV dysfunction, but the significance of frequent PVCs in asymptomatic patients with normal LV function remained uncertain.<sup>13,14</sup> To address this, Niwano et al<sup>13</sup> conducted a study involving 239 patients who presented with frequent PVCs (defined as more than 1000 beats per day) originating from either the right or LVOT but without any detectable heart disease. Echocardiography and CMR imaging were performed to rule out structural heart disease, and Holter-ECG monitoring was repeated 2 or 3 times to assess the prevalence of PVCs. The findings revealed that over a follow-up period of 5.6 years, none of the patients experienced any significant cardiac events. Although there were no changes in the mean left ventricle ejection fraction (LVEF) and left ventricle diastolic dimension (LVDd) in the entire cohort, a tendency toward a lower EF and a higher LVDd was observed in patients with a high PVC burden ( $P < .001$ ).<sup>13,15</sup> However, Yarlagadda et al<sup>16</sup> reached a different conclusion in a smaller cohort study. They enlisted 27 patients with frequent PVCs originating from RVOT (mean burden of  $17\,624 \pm 12\,611$  PVCs) who underwent assessment of cardiac structure and function (all patients were investigated by echocardiography and 8 patients were also investigated by CMR) before catheter ablation. Following ablation, patients were reassessed with echocardiography and Holter monitoring. Patients with reduced EF tended to be older compared to those with normal function ( $58 \pm 14$  years vs.  $42 \pm 18$  years;  $P = .013$ ). However, the PVC burden was similar between patients with preserved ventricular function ( $17\,859 \pm 13\,488$  ectopic beats per 24 hours) and those with impaired function ( $17\,541 \pm 11\,479$  ectopic beats per 24 hours;  $P = .800$ ). A successful ablation procedure was conducted in 23 patients (85%), and among those with reduced EF, an improvement in the EF was observed (from  $39 \pm 6\%$  to  $62 \pm 6\%$ ;  $P = .017$ ). This study led to the idea that repetitive PVCs originating from RVOT may be an unrecognized cause of cardiomyopathy.<sup>16</sup> Baman et al<sup>17</sup>, in a study which included 174 patients referred for an ablation procedure for frequent PVC (mean PVC burden of  $20\% \pm 16\%$  determined by 24-hour Holter monitoring) reached a similar conclusion. In total, 57 patients (33%) showed a reduced LVEF, averaging  $37\% \pm 10\%$ . Those with decreased EF had a mean PVCs burden of  $33\% \pm 13\%$ , while those with normal left ventricular function had a burden of  $13\% \pm 12\%$  ( $P < .0001$ ). A PVC burden greater than 24% effectively separated patients with impaired vs. preserved left ventricular function (sensitivity 79%, specificity 78%, AUC 0.89). The minimum PVC burden leading to reversible cardiomyopathy was found to be 10%, and they concluded that PVC burden emerged as an independent factor associated with PVC-induced cardiomyopathy (HR 1.12, 95% CI 1.08-1.16;  $P < .01$ ).<sup>17</sup>

Concerning patients with structural heart disease (SHD), Sarrazin et al<sup>18</sup> included in their study 30 patients with myocardial infarction (mean LVEF of  $36\% \pm 12\%$  assessed by transthoracic echocardiography) who were evaluated

### HIGHLIGHTS

- Cardiac magnetic resonance can detect subtle changes in patients with idiopathic PVCs.
- The presence of late gadolinium enhancement in patients with idiopathic PVCs can influence the prognosis of these individuals.
- In some patients with idiopathic PVCs, given the characteristics of the scar, cardiac magnetic resonance can help with arrhythmic risk stratification.



**Figure 1. Types of premature ventricular contractions based on origin. LVOT, left ventricle outflow tract; LV, left ventricle; RVOT, right ventricle outflow tract; RV, right ventricle.**

for implantation of implantable cardioverter defibrillator (ICD). In total, 15 patients with a high PVC burden (at least 5% on 24-h Holter) underwent ablation of PVCs before ICD implantation and the remaining 15 patients served as a control group. Scar burden was evaluated by CMR with late gadolinium enhancement (LGE) in both groups. The PVC ablation procedure was successful in all 15 patients, effectively reducing the average PVC burden from  $22\% \pm 12\%$  to  $2.6\% \pm 5.0\%$  ( $P < .001$ ). Following the intervention, there was a notable increase in LVEF from  $38\% \pm 10\%$  to  $51\% \pm 9\%$  among the patients who underwent PVC ablation ( $P = .0001$ ). In contrast, in the control group, LVEF showed no significant change during the same timeframe ( $34\% \pm 14\%$  vs.  $33\% \pm 15\%$ ;  $P = .6$ ). Additionally, patients with a higher PVC burden exhibited a smaller scar burden by LGE-CMR in comparison to the control patients.<sup>18</sup>

Robust data regarding the prognostic impact of PVCs comes from a meta-analysis conducted by Ataklte et al<sup>19</sup>, which included 11 studies and 106 195 individuals with PVCs, focusing on the relationship between PVCs and SCD. The prevalence of frequent PVCs, defined as more than 1 PVC on a 2-minute ECG recording, in the included studies varied from 1.2% to 10.7%. The overall risk of SCD was found to be 2.64 times higher in individuals with frequent PVCs compared to those without frequent PVCs (HR 2.64, 95% CI 1.93-3.63,  $P = .469$ ). A limitation of this meta-analysis was that although certain studies aimed at including only patients without structural heart disease, this classification was based only on their clinical history, without additional investigation.<sup>19</sup> Dukes et al<sup>20</sup> conducted their study on a population-based sample that revealed a correlation between a higher occurrence of PVCs and a decrease in LVEF, an elevated risk of developing congestive heart failure (CHF), and increased mortality. Comparing individuals in the upper quartile of PVC burden to those in the lowest quartile, after a median follow-up of over 13 years, the former group had a 3-fold higher risk of experiencing a 5-year decline in LVEF (OR: 3.10, 95% CI: 1.42-6.77,  $P = .005$ ), a 48% increased risk of incident CHF (HR: 1.48,

95% CI: 1.08-2.04,  $P = .02$ ), and a 31% increased risk of death (HR: 1.31, 95% CI: 1.06-1.63,  $P = .01$ ). Given that PVCs may benefit from medical or ablative therapy, PVCs may represent a modifiable risk factor for developing CHF and mortality.<sup>20,21</sup> The origin of the PVCs seems to also play a role as a prognostic marker, since Del Carpio Munoz et al<sup>22</sup> observed that PVCs arising from the LV were linked with a significant reduction in LVEF at a PVC burden greater than 20%, while PVCs developing from the right ventricle (RV) were associated with an important reduction in LVEF at a PVC burden of at least 10%.<sup>8,22,23</sup>

This initial data pointing toward a prognostic impact of “benign” PVCs represents the basis for further research of the electroanatomic substrate of this arrhythmia.

### Cardiac Magnetic Resonance and Premature Ventricular Contractions

In the last decades, CMR has been used as a useful imaging technique in a great number of cardiac diseases, being able to precisely and reproducibly determine ventricular volumes, structure, and function.<sup>24</sup> Several studies concluded that CMR-detected scar may be associated with ventricular abnormalities and that they might predict adverse outcomes in patients presenting with a greater PVC burden (Table 1).

It has been postulated since the 90s that CMR can demonstrate subtle morphological changes in the myocardium, even in patients with “benign” arrhythmias, such as RVOT tachycardia. To address this issue, Globits et al included 20 patients addressed for catheter ablation of recurrent RVOT tachycardia, who were investigated prior to the procedure by CMR. Ten healthy individuals, matched in terms of both age and sex, were used as control subjects. The effective ablation sites were compared with CMR findings. Among the control subjects, abnormalities in the RV were observed only in 2 out of 10 individuals (prominent fatty deposits). In contrast, CMR scans revealed morphological alterations in the RV free wall in 13 out of 20 patients (65%) with RVOT tachycardia. These changes consisted of the presence of

**Table 1. Correlation between Frequent PVCs and CMR Abnormalities (Literature Review)**

Study	Year	No. of Patients	CMR Abnormalities	PVC Origin	Results
Aquaro et al <sup>26</sup>	2010	396	61 (13.8%)	RVOT or higher portion of the interventricular septum	Patients with multiple RV abnormalities had worse outcome than those with no abnormalities (HR: 48.6; 95% CI: 6.1-384.8; $P < .001$ ).
Yokokawa et al <sup>27</sup>	2017	321	67 (20%)	LV and RV	The combination of SHD findings by MRI and VT inducibility conferred independently an increased risk of adverse outcome (multivariate hazard ratio 25.73, 95% CI: 6.74-98.20, $P < .001$ ).
Penela et al <sup>28</sup>	2019	70	29 (41.4%)	LV and RV	The mass of myocardial scar influences but does not prevent the probability of response to PVC ablation [OR 0.9 (0.81-0.99), $P = .04$ ].
Ghannam et al <sup>29</sup>	2020	272	67 (24.6%)	LV and RV	The presence and the amount of LGE at CMR was related to the risk of VT occurrence independent of EF (HR 18.8 [2.0-176.6], $P = .01$ and HR 1.4 [1.1-1.7]/cm <sup>3</sup> scar, $P < .001$ ).
Ghannam et al <sup>7</sup>	2020	99	99 (100%)	LV and RV	Patients with greater scar burden were associated with inducibility of VT independent of EF or prior history of VT (adjusted OR 1.67 [1.24-2.24]/cm <sup>3</sup> , $P < .01$ ).
Muser et al <sup>1</sup>	2020	518	85 (16%)	LV and RV	Presence of myocardial abnormalities on CMR predict worse clinical outcomes ( $P < .01$ ).
Ghannam et al <sup>30</sup>	2021	333	112 (34%)	LV and RV	Risk scores can help distinguish between patients at high and low risk for the presence of cardiac scar and worse arrhythmia outcomes based on age (OR 1.02 [1.01-1.04]/year, $P = .019$ ) and pre-ablation EF (OR 0.92 [0.89-0.94]/%, $P < .001$ ).
Nikolaidou et al <sup>31</sup>	2021	72	39 (54.2%)	LV and RV	Abnormalities revealed by CMR in patients with PVC can be related to PVC induced cardiomyopathy.
Hosseini et al <sup>32</sup>	2022	255	35 (13.7%)	LV and RV	1 in 7 patients included in the study with frequent PVCs and no known structural heart disease had myocardial abnormality detected on CMR (HR: 4.35; 95% CI: 1.34-14.15; $P = .014$ ).

CMR, cardiac magnetic resonance; EF, ejection fraction; LGE, late gadolinium enhancement; LV, left ventricle; PVC, premature ventricular contraction; RV, right ventricle; RVOT, right ventricle outflow tract; SHD, structural heart disease; VT, ventricular tachycardia.

fatty tissue (5 patients), thinning of the wall (9 patients), and dyskinetic wall segments (4 patients). Eight of these patients displayed extra fat deposits, thinning, or a saccular aneurysm in the RV outflow tract and in 6 of these cases, these findings correlated with the location of the ablation site.<sup>25</sup>

In a study conducted in 2015 in the United States, a group of 1840 participants without clinically apparent cardiovascular disease (mean age 68) underwent LGE-CMR to identify myocardial scars. The results showed that 146 participants (7.9%) had myocardial scars. Surprisingly, 114 (78%) of the patients were classified as "normal" by the electrocardiogram, echocardiography, and clinical examination.<sup>33</sup>

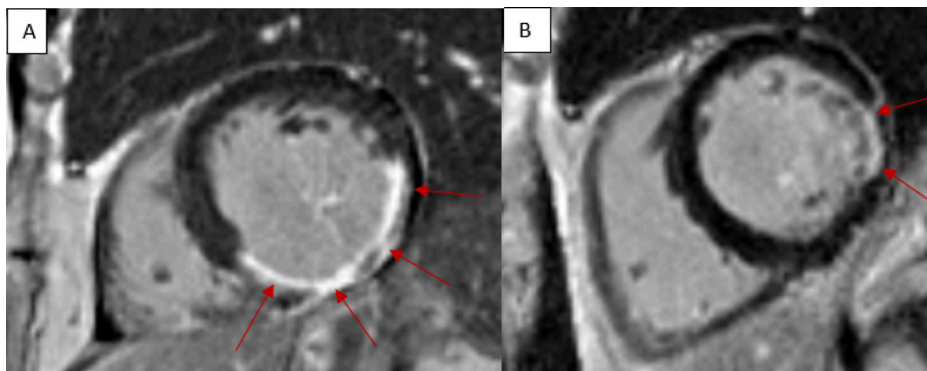
### Cardiac Magnetic Resonance and Late Gadolinium Enhancement in Patients with Premature Ventricular Contractions

Late gadolinium enhancement cardiac magnetic resonance represents nowadays one of the most valuable imaging tools in modern cardiology, with an impact on the diagnostic and risk stratification of both ischemic and non-ischemic cardiomyopathies. Cardiac magnetic resonance, particularly when used with LGE sequences and quantitative measures like T1-mapping, both native and with extracellular

volume fraction measurement, as well as T2-mapping and T2-\*mapping, has been validated across a broad spectrum of clinical scenarios through comparison with histological findings. Cardiac magnetic resonance allows for both qualitative and quantitative assessment of individual myocardial scar tissue and fibrosis. Cardiac magnetic resonance techniques proved to be especially valuable in cases where the underlying cause of unclear cardiomyopathy, whether ischemic or non-ischemic, needs to be determined without invasive procedures. By examining the localization and distribution patterns of scars and/or fibrosis, non-invasive CMR can aid in determining the presumed underlying cause (Figure 2).<sup>34-36</sup>

With the aim of studying the prevalence of scar detected by CMR in patients without previously known cardiac disease, Ghannam et al included 272 patients with frequent PVCs (mean PVC burden of 20.4% ± 13.0%) and observed that LGE was present in 67 patients (25%). Patients with scar tissue detectable by CMR were older, predominantly male, with comorbidities such as arterial hypertension and chronic obstructive pulmonary disease (COPD). Additionally, they had a lower baseline EF. The majority of these patients, 64 out of 67 (96%), exhibited exclusively intramural scarring.





**Figure 2. Presence of cardiac scar in the inferior and lateral walls of LV (A) and anterolateral wall (B); LV, left ventricle.**

The remaining 3 patients had scar tissue in the papillary muscles, transmural scar on the lateral left ventricular free wall, and epicardial scar near the anterior basal septum. However, the primary scar was predominantly located in the basal septum (62 out of 67, 93%) and all patients with multifocal scar tissue had a component of basal septal scarring. All patients were submitted to programmed ventricular stimulation (PVS) and were observed for the development of VAs. Among the studied group, 7 patients (3%) exhibited inducible VT. The correlation between the extent of LGE-CMR scar and the likelihood of long-term VT occurrence was established, irrespective of EF [HR 18.8 (2.0-176.6),  $P = .01$  and HR 1.4 [1.1-1.7]/cm<sup>3</sup> of scar,  $P < .001$ , respectively]. The positive and negative predictive value of PVS for VT during long-term follow-up reached percentages of 71% and 100% respectively.<sup>29</sup>

In a study involving 76 patients with VAs (Lown classification  $\geq 2$ ), who had no known cardiac disease following standard diagnostic procedures, and underwent CMR imaging. Among these patients, 44 out of 76 showed abnormal findings on CMR. Notably, in 24 out of 76 cases, CMR revealed pathology that was not detected by echocardiography and for 20 patients the final diagnosis was based on the CMR pattern. Furthermore, in 7 patients, the location of CMR-detected abnormalities (scars) directly corresponded to the origin of the ventricular arrhythmias. The identification of these CMR findings prompted changes in treatment for 21 patients and/or additional diagnostic procedures for 8 patients. The study concluded that in some patients, subtle changes detected by CMR often serve as significant contributors to VAs, as evidenced by scar morphology.<sup>37</sup>

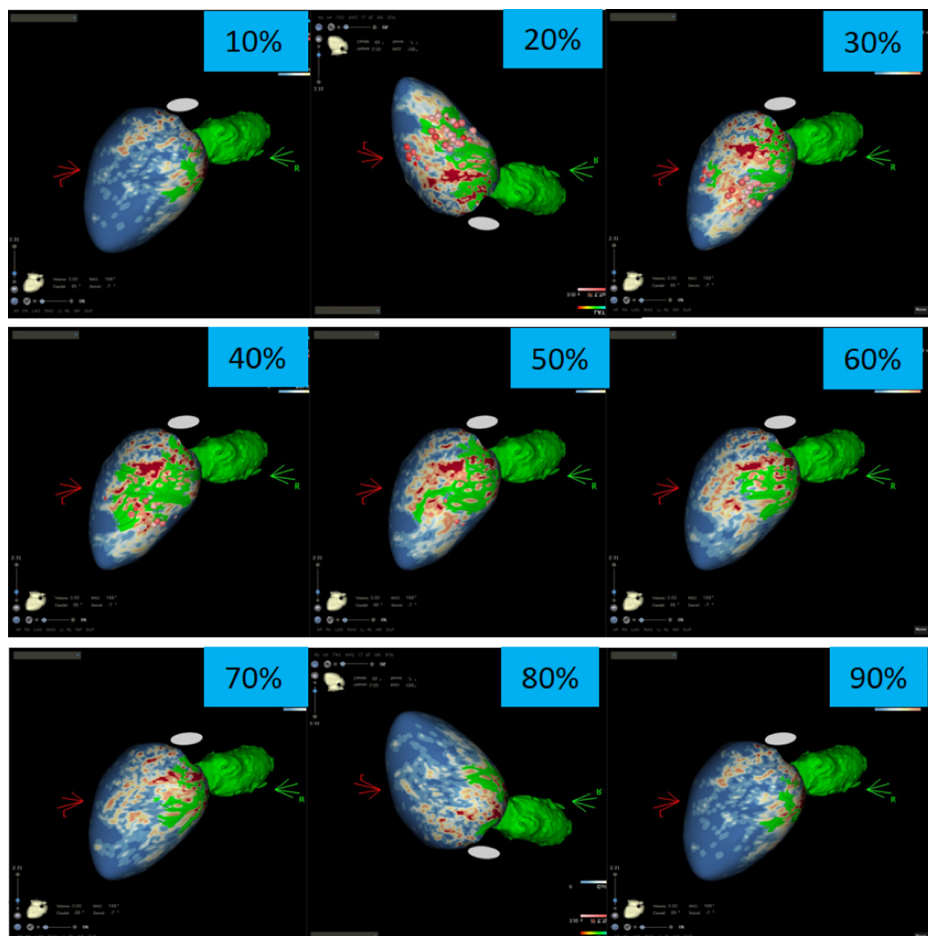
In an elaborate study conducted by Andreini et al, a total of 946 patients exhibiting significant ventricular arrhythmias (defined as  $>1000$  PVCs/24 hours, nonsustained VT, sustained ventricular tachycardia, or a history of resuscitated cardiac arrest) and showing no pathological findings on echocardiography were included. The mean age of the participants was  $41 \pm 16$  years, with 64% being men. Cardiac magnetic resonance studies revealed SHD in 241 patients (25.5%) and abnormal findings not specific for a definitive SHD diagnosis in 187 patients (19.7%). The most prevalent conditions were myocarditis ( $n = 91$ ), arrhythmogenic cardiomyopathy ( $n = 55$ ), dilated cardiomyopathy ( $n = 39$ ), ischemic heart disease ( $n = 22$ ), hypertrophic cardiomyopathy ( $n = 13$ ),

congenital cardiac disease ( $n = 10$ ), left ventricle noncompaction ( $n = 5$ ), and pericarditis ( $n = 5$ ). The study also concluded that CMR imaging could identify SHD in a significant proportion of patients with significant ventricular arrhythmias, despite having normal echocardiography results, based on scar characteristics.<sup>38</sup>

The role of CMR is of extreme importance also for detecting RV pathology in patients with PVCs (Figure 3). In individuals who have both frequent PVCs (defined as at least 5% PVCs in 24 h on any ambulatory ECG monitoring) and multiple RV abnormalities (RVA), such as RV dilatation, fat infiltration, and wall motion abnormalities, experienced poorer outcomes compared to a group without RVA (HR: 48.6; 95% CI: 6.1-384.8;  $P < .001$ ). Out of the 61 patients in the RVA-2 group, only 6 received a definite diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC) based on the 2010 Task Force Criteria. Additionally, individuals with a single imaging criterion for RVA exhibited worse outcomes compared to those without any RVA. Furthermore, patients with wall motion abnormalities in the RV had a higher prevalence of cardiac events compared to the group without RVA (HR: 27.2; 95% CI: 3.0-244.0;  $P = .03$ ).<sup>26,39</sup> In support of this data, in a study published by Hosseini et al<sup>32</sup>, which included a total of 225 participants with frequent PVCs, 35 had myocardial abnormalities detected by CMR, 28 patients had evidence of LV LGE, out of whom, in 14 patients, the localization of the scar correlated to the origin of the PVCs. They concluded that patients with frequent PVCs who are not known to have any type of structural heart disease but are identified with LGE at CMR have a worse long-term outcome of all-cause mortality, nonfatal episode of ventricular fibrillation or VT, and reduction in LVEF of  $\geq 10\%$  compared to baseline LVEF (HR: 4.35; 95% CI: 1.34-14.15;  $P = .014$ ).<sup>32</sup>

#### **Myocardial Scar and Major Adverse Cardiac Events**

Despite all the data we reported before, there remains the question of whether the presence of LGE in patients with PVCs can be considered a risk factor for future major adverse cardiovascular event (MACE), or just the anatomical substrate. Muser et al<sup>1</sup> identified that among the 518 patients included in the study, with at least 1000 PVCs/24 h, otherwise normal 12 lead surface electrocardiogram (ECG), normal transthoracic echocardiography and absence of significant coronary artery disease, myocardial abnormalities were



**Figure 3.** Integration of CMR images for the electroanatomical mapping in a patient with PVCs originating in the RV—extensive epicardial scar tissue at the level of the RVOT.

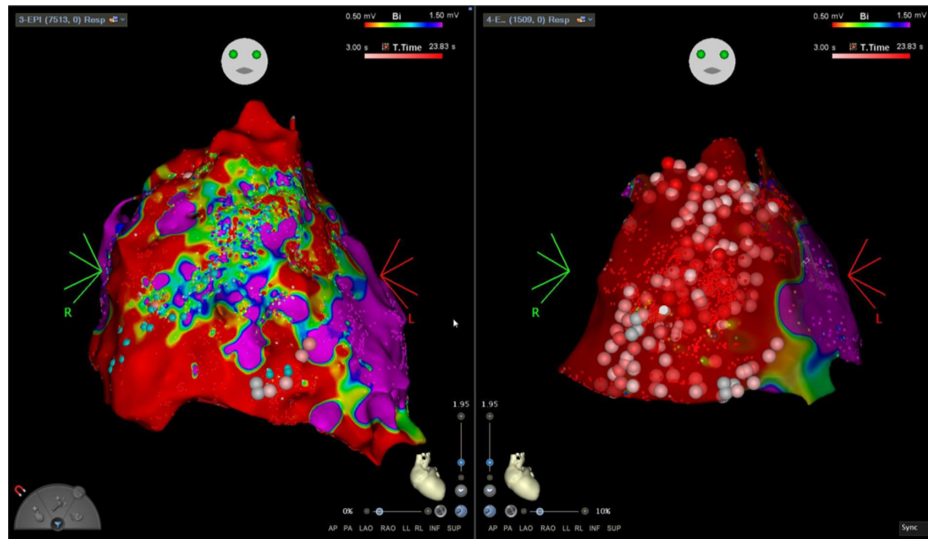
detected by CMR in 85 individuals (16%) who had more than 1000 PVCs within a 24-hour period. After a median follow-up duration of 67 months, a composite endpoint comprising SCD, resuscitated cardiac arrest, nonfatal episodes of ventricular fibrillation or sustained VT that required appropriate implantable cardioverter-defibrillator therapy occurred in 26 patients (5%,  $P < .01$ ). The incidence of this composite outcome was significantly higher among subjects with myocardial abnormalities observed on CMR imaging, with 25 individuals (29%) experiencing the outcome, compared to only 1 individual (0.2%) without such abnormalities ( $P < .01$ ).<sup>1</sup> In a similar study, Nikolaidou et al<sup>31</sup> included 72 patients with frequent PVCs (>500/24 h) and otherwise normal ECG, echocardiography and no coronary artery disease who were investigated by CMR and reached a similar verdict. Out of the 72 patients, 20.8% were diagnosed with possible PVC-induced cardiomyopathy ( $P < .001$ ).

In patients with structural heart disease, CMR can help with measuring the ventricular function and volumes, detection, and quantification of LGE, with the aim of better risk stratification. Neilan et al<sup>40</sup> included in their study a population of 137 patients with aborted SCD who underwent CMR investigation. Out of the 137 patients, 98 patients had LGE (subendocardial in 47%, transmural in 21%, mid-myocardial in 23%,

epicardial in 8%, and at the insertion point of the RV in 1 of the patients), with a median amount of LGE of 9.9% of the LV myocardial mass. In total, 104 patients were discovered with a potential arrhythmic substrate: an infarct-pattern LGE in 60 patients (44%), non-infarct LGE in 21 patients (19%), and active myocarditis in 14 patients (10%). The strongest predictors of recurrent events were the presence of LGE (adjusted HR: 6.7; 95% CI: 2.38-18.85;  $P < .001$ ) and the extent of LGE (HR: 1.15; 95% CI: 1.11-1.19;  $P < .001$ ).<sup>40</sup>

#### Scar Anatomy and Arrhythmic Risk in Patients with Premature Ventricular Contractions

Apart from the presence of LGE, the anatomy of the scar plays an important role for the management of patients with PVCs. Channels of heterogeneous tissue within the scar, connecting to healthy tissue as identified in LGE-CMR, are more prevalent in patients experiencing VT (88% compared to 33%) (Figure 4). This suggests a potential association with the arrhythmic risk. Subsequent investigations utilizing 3-T scans and specialized imaging software confirmed the effectiveness of LGE-CMR in detecting these channels. This was not only in comparison to electroanatomical voltage maps but also by analyzing electrogram characteristics within the conducting channels. The conducting channels identified by PSI (pixel signal intensity) maps coincided with areas of late



**Figure 4. Scar analysis (from the endocardium to the epicardium) with dedicated software for the detection of the arrhythmic channels. Blue—normal tissue; red—fibrosis; green—arrhythmic channels.**

potentials in the electroanatomical maps, confirming slow conduction. Additionally, LGE-CMR's ability to distinguish scar tissue within the endocardium, mid-myocardium, and epicardium revealed a 3-dimensional structure of the scar. LGE-CMR demonstrated superior capability in detecting the 3-dimensional pathway of conducting channels, showing higher concordance and improved border zone detection compared to conventional 2-dimensional LGE-CMR.<sup>41-43</sup>

In a study conducted by Lin et al<sup>44</sup>, a total of 63 patients with LVEF below 50% and with LGE detected by CMR were included. After a median follow-up period of 1379 days, 8 patients experienced VT/VF episodes, and 14 patients died. Among the CMR-measured parameters, only the likelihood of detecting conducting channels (CCs) via LGE-CMR was higher in patients with VT/VF compared to those without VT/VF (75.0% vs. 16.4%,  $P < .001$ ). Similarly, the probability of identifying the CC was higher in the group that died (50.0% vs. 16.3%,  $P = .004$ ). Other LGE-CMR variables did not reach statistical significance. In the univariate Cox regression model, the identification of CC was positively correlated with VT/VF episodes (HR: 27.032, 95% CI: 3.291-222.054,  $P = .002$ ) and increased overall mortality (HR: 4.766, 95% CI: 1.643-13.824,  $P = .004$ ). Conversely, LVEF demonstrated an inverse association with VT/VF episodes (HR: 0.119, 95% CI: 0.015-0.977,  $P = .048$ ) and increased overall mortality (HR: 0.491, 95% CI: 0.261-0.925,  $P = .028$ ) during the follow-up period and concluded that CC identification using LGE-CMR can help pinpoint heart failure patients at risk for VT/VF.<sup>44</sup>

In patients with nonischemic cardiomyopathy who presented with intramural scar and who were referred for an ablation procedure of VA (patients with either PVCs and no history of VT or patients with documented VT), the characteristics of the scar influenced the result of the procedure. Patients lacking clinical or inducible VT exhibited smaller overall and core scar dimensions compared to those with a VT history or inducible VT (total scar: 1.12 [0.74-1.79]/cm<sup>3</sup> vs. 7.45 [4.16-12.21]/cm<sup>3</sup>,  $P < .001$ ). A total scar volume of at least

2.78 cm<sup>3</sup> correlated with VT inducibility (95% CI [0.89-0.98], sensitivity 85%, specificity 90%). They concluded that the assessment of scar size in patients with intramural scarring helps in risk evaluation for nonischemic cardiomyopathy and VAs, irrespective of EF or previous VT (adjusted OR 1.67 [1.24-2.24]/cm<sup>3</sup>,  $P < .01$ ).<sup>7</sup>

#### **Novel Cardiac Magnetic Resonance Sequences for Detecting the Site of Origin of the Premature Ventricular Contractions**

Acquiring high-resolution imaging is essential for detecting smaller scar regions and enhancing the assessment of scar geometry in patients undergoing VT or PVCs ablation.<sup>45</sup> The incorporation of image acceleration techniques, such as compressed sensing, has facilitated quicker acquisition of 3D imaging with higher spatial resolution (1.2 mm<sup>3</sup>), maintaining acceptable scan duration and image quality while demonstrating comparable scar characteristics to conventional 3D LGE imaging.<sup>46</sup> Additionally, parallel imaging using a stack-of-spirals acquisition technique has enabled rapid 3D LGE acquisitions within a 12-heartbeat breath-hold.<sup>47</sup> Three-dimensional free-breathing self-navigating magnetic resonance sequences have been developed to address issues associated with respiratory navigator placement and irregular breathing patterns, enabling high-resolution visualization of scar distribution and improved delineation of scar borders.<sup>48</sup> Another emerging technique, super-resolution reconstruction, reconstructs a high-resolution image from multiple low-resolution views of the same volume, demonstrating good agreement with the bipolar voltage range of scar border zone.<sup>49</sup> The introduction of dark-blood LGE sequences as a technical solution to suboptimal contrast between scar and the blood pool holds promise for improved substrate assessment. These sequences have been designed to concurrently decrease signal intensity from normal myocardium and the blood pool while enhancing contrast between scar and blood, while also preserving contrast between scar and myocardium. Given that a significant

proportion of VTs originate in the sub-endocardial region, improved contrast between scar and the blood pool could enhance substrate detection in these regions.<sup>50</sup>

### Quantification of Scar Volume by Cardiac Magnetic Resonance

The physiological mechanism underlying LGE of myocardial fibrosis results from 2 main factors: an expanded volume of distribution for the contrast agent and a lengthened wash-out period due to reduced capillary density within the fibrotic myocardial tissue. This combination leads to an elevation in gadolinium concentration within the fibrotic regions, resulting in T1 shortening. Consequently, these areas manifest as bright signal intensity in CMR images using conventional inversion-recovery gradient echo sequences.<sup>51,52</sup> Scar volume can influence the arrhythmic risk, as previously described above.

In a study involving 40 patients with hypertrophic cardiomyopathy (mean age 48 years, 30 males) and 20 normal subjects (mean age 38 years, 16 males), who underwent CMR, 3 methods for quantifying LGE were compared. Firstly, the standard deviation (SD) 2 method involved placing a region of interest (ROI) within normal myocardium and defining enhanced myocardium as having signal intensity more than 2 standard deviations above the mean of the ROI. Secondly, the SD 6 method defined enhanced myocardium with a threshold of 6 SD above the mean of the ROI. Thirdly, in the RC method, an ROI was placed in the background of the image, and a Rayleigh curve was generated using the SD of that ROI, serving as an ideal curve for the distribution of signal intensity in perfectly nulled myocardium. Results showed that patients with hypertrophic cardiomyopathy had lower concordance between the measured curve of signal intensity distribution and the Rayleigh curve compared to controls ( $63.7 \pm 12.3\%$  vs.  $92.2 \pm 2.3\%$ ,  $P < .0001$ ). A concordance cutoff of  $<82.9\%$  had a sensitivity of 97.1% and specificity of 92.3% in distinguishing hypertrophic cardiomyopathy from controls. The RC method yielded a higher score than the other methods. Although the average extent of enhanced myocardium measured by SD6 and the Rayleigh curve method did not significantly differ, the SD6 method underestimated enhancement in 12% and overestimated it in 5% of hypertrophic cardiomyopathy patients. The conclusion drawn was that quantifying fibrosis in LGE images using a cutoff derived from the Rayleigh curve is more accurate than using a fixed cutoff.<sup>53,54</sup>

Various methods are available for quantifying cardiac fibrosis volumes, including manual quantification, thresholding by different standard deviations (2, 3, 4, 5, or 6) above remote myocardium, and the full width at half maximum (FWHM) technique.<sup>55</sup> In a study led by Flett et al<sup>56</sup>, 60 patients with 3 different causes of LGE were scanned (acute myocardial infarction=20 patients, chronic myocardial infarction=20 patients, and hypertrophic cardiomyopathy=20 patients), and LGE volume was measured using 7 techniques. The study revealed significant variation in LGE volume depending on the quantification method employed. Notably, there was no statistically significant difference between LGE volume measured by the FWHM technique, manual quantification, and

the 6-SD or 5-SD techniques. However, the 2-SD technique produced LGE volumes up to twice as high as those obtained with the FWHM, 6-SD, and manual techniques. Additionally, reproducibility was poorer in hypertrophic cardiomyopathy compared to acute myocardial infarction or chronic myocardial infarction. The FWHM technique demonstrated the highest reproducibility across all 3 conditions compared to any other method ( $P < .001$ ). The conclusion reached by the authors was that irrespective of the underlying disease, the FWHM technique for LGE quantification yields similar results to manual quantification and demonstrates the highest statistical reproducibility, potentially reducing required sample sizes by up to half.<sup>56</sup>

In different studies which focused on myocarditis,<sup>57</sup> mitral valve prolapse,<sup>58</sup> and Fabry disease,<sup>59</sup> it was concluded that semi-automated grayscale thresholding techniques may be a feasible method for the quantification of cardiac fibrosis.

In a retrospective analysis of the DERIVATE registry, it was investigated whether post-infarct scar identified by LGE-CMR could be quantified fully automatically by machine learning algorithms. They also compared the predictive capabilities of LGE CMR scar analyzed by humans vs. machines in forecasting arrhythmic events. The findings revealed that machine-based assessment of dense or total scar provided additional predictive value beyond the guideline criterion for the association with MACE (AUC: 0.68 vs. 0.63,  $P = .02$  and AUC: 0.67 vs. 0.63,  $P = .01$ , respectively). When employing competing risks modeling, dense and total scar showed superior performance compared to the guideline-based risk criteria (AUC: 0.67 vs. 0.61,  $P = .01$  and AUC: 0.66 vs. 0.61,  $P = .005$ , respectively). The conclusion reached was that fully automatic machine learning-based analysis of LGE reliably quantifies myocardial scar mass.<sup>60</sup>

### Implications of Late Gadolinium Enhancement Detection for the Catheter Ablation Procedure

In regions where myocardial scar is detected, the presence of viable myocardial fibers within the scar causes the development of slow electrical pathways, creating a proper environment for the formation of reentrant circuits. By either eliminating or isolating this substrate, it is possible to potentially avoid the occurrence of different arrhythmias, especially after integration with the electroanatomical mapping (EAM).<sup>61-63</sup>

Several studies were conducted in order to determine whether CMR can also help prior to the ablation in the planning phase of the procedure. Ghanam et al<sup>30</sup> investigated 333 patients who underwent catheter ablation for PVCs (mean burden of  $20.7\% \pm 13.14$ ) and had no history of sustained ventricular arrhythmias or syncope and were investigated with CMR prior to the ablation. The study found that one-third of the patients referred for PVC ablation had cardiac scar. Through multiple logistic regression analysis, the researchers identified age (OR 1.02 [1.01-1.04]/year,  $P = .019$ ) and baseline EF as predictive factors for the presence of scar (OR 0.92 [0.89-0.94]/%,  $P < .001$ ). The study also determined the most common locations from which PVCs originated including: the outflow tracts (34%), intramural locations (17%),



epicardial locations (16%), papillary muscle locations (14%), and parahisian locations (5%). Patients with cardiac scar had a lower occurrence of PVCs originating from epicardial and outflow tract sources compared to those without scar (8.0% vs. 20.4%,  $P = .006$  and 25.0% vs. 38.5%,  $P = .02$ , respectively). Conversely, intramural sources were more prevalent in patients with scar compared to those without scar (39.3% vs. 6.3%,  $P < .001$ ). Following the ablation procedure, patients with cardiac scar experienced a higher burden of PVCs and a lower EF post ablation.<sup>30,64,65</sup> Penela et al<sup>28</sup> included in a study 70 patients with LV dysfunction (mean LVEF = 34%) and frequent PVCs (a mean PVC burden of 23%) who were admitted for catheter ablation procedures. All 70 patients underwent CMR investigation before the ablation procedure and in 29 patients, the LGE sequence identified scar in the myocardium with a median mass of scarring of 10.4 grams. Median scar mass was noticeably smaller in the patients in whom the procedure was a success, but the acute successful ablation rate was similar in the 2 groups (83% in the group with scar and 88% in the group without scar,  $P = .4$ ).<sup>28</sup>

In support of this data, Berrueto et al<sup>66</sup> included 101 patients with left ventricular scar-related VT defined as the presence of previous myocardial infarction, LV dilatation/systolic dysfunction, or normal LV diameters/systolic function with evidence of ventricular scar on LGE-CMR or EAM. All patients underwent a catheter ablation procedure for VT with conducting channels identification and subsequent channels elimination and concluded that after acquiring CMR images of the scar, scar dechanneling alone results in low recurrence and mortality in 54% of the patients despite the limited ablation extent and recurrences are mainly related to incomplete conducting channels elimination ( $P = .013$ ).<sup>66,67</sup> Andreu et al<sup>68</sup> included 30 patients with SHD (defined as the presence of myocardial scar at LGE-CMR) who were referred for VT ablation and compared different CMR methods of the scar. This was done using a navigator-gated 3D sequence (3D-GRE) and conventional 2D imaging techniques, employing either a single-shot inversion-recovery steady-state-free-precession (2D-SSFP) or an inversion-recovery gradient echo (2D-GRE) sequence. The scar components, including the core and border zone, were quantified using different thresholds of maximum pixel intensity (60% and 40%, respectively) in the analysis and each imaging sequence provided a 3D reconstruction of the scar. There were no notable differences in the mass of the scar core between the 2D-GRE, 2D-SSFP, and 3D-GRE sequences (mean values of 7.48 + 6.68, 8.26 + 5.69, and 6.26 + 4.37 grams, respectively;  $P = .084$ ). However, the mass of the border zone was smaller in the 2D-GRE and 2D-SSFP sequences compared to the 3D-GRE sequence (9.22 + 5.97 and 9.39 + 6.33 vs. 10.92 + 5.98 grams, respectively;  $P = .042$ ). When comparing the observed critical components in the EAM to the 3D-GRE sequence, a match was found in 79.2% of cases. However, this matching decreased to 61.8% and 37.7% when comparing the EAM to the 2D-GRE and 2D-SSFP sequences.<sup>68</sup> In another study published by Yokonawa et al that comprised 321 patients with frequent PVCs, that were investigated by CMR prior to catheter ablation, it was noticed that LGE was present in 60

patients and SHD was present in 64 patients, defined as the LGE pattern of previous myocardial infarction, non-ischemic cardiomyopathy (NICM), RV dilatation and dyskinesia, LV non-compaction, and congenital LV aneurysm. Sustained monomorphic VT was induced in 15 patients. After a median follow-up period of 20 months, the primary endpoint of VT/VF or death occurred in 15. The combination of SHD identified by MRI and VT inducibility granted independently an increased risk of adverse outcome (multivariate HR 25.73, 95% CI: 6.74-98.20,  $P < .001$ ), concluding that pre-ablation CMR and programmed stimulation can be useful for risk stratification in patients with frequent PVCs.<sup>27,69</sup>

Using LGE-CMR for planning ablation procedures proves particularly beneficial in assessing scar location and determining the most suitable ablation strategy.<sup>41</sup> In this regard, a non-randomized study conducted by Acosta et al<sup>70</sup> demonstrated that ischemic patients with epicardial substrate, identified through imaging techniques, who underwent epicardial access experienced superior outcomes in terms of VT recurrence compared to those who solely underwent the endocardial approach. Moreover, the relevance of scar location in NICM patients has also been underscored in guiding the ablation procedure, as it correlates with the type of arrhythmia and the chosen ablation approach.<sup>71</sup> This aspect was further validated in a larger study involving 80 patients encompassing both ischemic cardiomyopathy (ICM) and NICM. In this study, the decision between the endocardial or epicardial approach was guided by imaging findings, and access to intramural substrate (within the left and/or right ventricle) was determined based on the proximity of the scar to the left and right endocardium.<sup>67</sup>

Bogun et al conducted CE-CMR on 29 patients with NICM, identifying scar tissue in 14 patients, 9 of whom experienced monomorphic VTs and 5 expressed PVCs. All 14 patients underwent a catheter ablation, resulting in a successful outcome for 9 of them. Among these 9 patients, 5 solely had endocardial scar, necessitating only endocardial ablation. However, in the remaining 4 patients, the scar was either intramural and epicardial or solely epicardial. Consequently, all 4 patients required an epicardial approach for effective therapy. These findings suggest that CE-CMR's scar localization can lead the decision on whether to pursue epicardial access for catheter ablation of VT.<sup>72</sup>

### Cardiac Magnetic Resonance After the Catheter Ablation Procedure

It was postulated by different authors that CMR may also be used to determine the effectiveness of catheter ablation for VA. Dinov et al noticed that following VA ablation, CMR revealed unenhanced lesions that resembled the no-reflow phenomenon observed in myocardial infarction. They enrolled 25 patients who were studied by CMR before and after a catheter ablation procedure for sustained VT. The dimensions and extent of radiofrequency injury were linked to the energy applied ( $r = 0.598$ ,  $P = .002$ ) during ablation and the drop in impedance ( $r = 0.416$ ,  $P = .038$ ) and in the failed procedures, the lesions' volume was insignificantly larger ( $3.86 \pm 3.3\%$  vs.  $2.6 \pm 1.7\%$ ,  $P = .197$ ), however, it was

considerably deeper ( $86 \pm 13\%$  vs.  $62 \pm 26\%$ ,  $P=0.03$ ), but the lesions did not appear to be connected to the immediate success of the ablation procedure.<sup>73</sup> In addition, Ilg et al<sup>74</sup> noticed in a study which included 35 patients without SHD who were addressed for ablation of VAs and investigated before and after the procedure by CMR, that radiofrequency ablation lesions can be detected long term after an ablation procedure targeting ventricular arrhythmias in patients without previous infarction. In 25 of the 35 patients (71%), ablation lesions were identified for a mean of  $22 \pm 12$  months by CMR and the ablation duration correlated with lesion size ( $r = 0.67$ ,  $P < .001$ ).<sup>74</sup> Dabbagh et al<sup>75</sup> observed in a study of 17 patients with repeat ablation procedure for VT, that ablation lesions can be detected by CMR after VT ablation for many months ( $36 \pm 29$  months) in post-infarction patients and have a different appearance than scar tissue (confluent subendocardial dark core), with no conductivity in repeat procedures suggesting that dark core may indicate effective ablative lesions, as the CMR dark core was closely correlated with the size of the area of unexcitability ( $R=0.98$ ;  $P < .001$ ).<sup>75,76</sup>

## CONCLUSION

In conclusion, in recent decades, the perspective on PVCs has shifted as multiple studies have pointed out the role that PVCs may play in the development of LV dysfunction and in the onset or progression of heart failure. Cardiac magnetic resonance developed as an important tool for the detection of subtle structural changes in the myocardium in patients with frequent PVCs, that represent predictors of worse long-term outcomes and can help with risk stratification.

**Ethics Committee Approval:** There is no need for ethics approval or informed consent for a narrative review.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Ş.A., L.Ş., G.S., and C.U. were responsible for the concept and design of the study. C.U. and G.S. were responsible for draft preparation. C.U., G.S., C.S., A.C., and R.A.S. were responsible for the review and editing of the manuscript. C.S., Ş.A., N.S., and L.Ş. were responsible for final draft visualization. C.U., G.S., M.G., and Ş.A. were responsible for the revision of the manuscript. All authors have read and agreed to the published version of the manuscript.

**Declaration of Interests:** The authors have no conflicts of interest to declare.

**Funding:** The authors declare that this study received no financial support.

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