Cardiac magnetic resonance reveals concealed structural heart disease in patients with frequent premature ventricular contractions and normal echocardiography: A systematic review

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ABSTRACT

Premature ventricular contractions (PVCs) are a common form of arrhythmic events, often representing an idiopathic and benign condition without further therapeutic interventions. However, in certain circumstances PVCs may represent the epiphenomenon of a concealed structural heart disease (SHD). Surface 12-leads EKG and 24-h dynamic EKG are necessary to assess their main characteristics such as site of origin, frequency and complexity. Echocardiography represents the first-line imaging tool recommended to evaluate cardiac structures and function. Cardiac Magnetic Resonance (CMR) is recognized as a superior modality for detecting structural cardiac alterations, that might evade detection by conventional echocardiography. Moreover, in specific populations such as athletes, CMR may have a crucial role to exclude a concealed SHD and the risk of serious arrhythmic events during sport activity. Some clinical characteristics such as male sex, older age or family history of sudden cardiac death (SCD) or cardiomyopathy, and some electrocardiographic features of PVCs, in particular a right branch bundle block (RBBB) with superior/intermediate axis morphology, the reproducibility of VAs during exercise test (ET) or the evidence of complex ventricular arrhythmias, may warrant a CMR evaluation, due to the high probability of SHD. In this systematic review our objective was to provide an exhaustive overview on the role of CMR in detecting a concealed SHD in patients with high daily burden of PVCs and a normal echocardiographic evaluation, paving the way for a more extensive utilization of CMR in presence of certain high-risk clinical and/or EKG features identified during the diagnostic workup.

1. Introduction

Premature ventricular contractions (PVCs) are part of ventricular arrhythmical phenomena frequently observed in clinical practice yet their relevance remains ambiguous. Their prevalence is approximately 3% to 30% in the general population, with various studies indicating a higher incidence in men compared to females and in elderly individuals aged >75 years [1]. In majority of cases, PVCs are benign and observed in structurally normal hearts without requiring further diagnostic or therapeutic interventions, unless accompanied by symptoms [2]. Conversely, in a subgroup of patients, PVCs may represent the manifestation of structural heart disease (SHD) undetected by the routine diagnostic assessments, including clinical examination, electrocardiography (EKG) and echocardiography. In such instances, accurate interpretation of the underlying, unseen structural cause becomes a paramount to prevent malignant ventricular arrhythmias (VAs) triggered by PVCs. It also facilitates the precise diagnosis of a specific cardiac disease, subsequently guiding tailored therapeutic strategies.

Echocardiography is the preferred imaging modality for initial assessments due to its safety, relatively low cost, and widespread availability [2–8]. However, cardiac magnetic resonance (CMR) offers superior resolution, enabling the detection of abnormalities such as ischemic disease, myocarditis, or cardiomyopathies [9–12]. In this contest, a key advantage of CMR is its ability to identify areas of myocardial fibrosis using late gadolinium enhancement (LGE) sequences, along with the fine assessment of cardiac anatomical structures [13,14]. It is well known that scar-related areas may serve as triggers for PVCs or, even worse, life-threating VAs. Consequently, the identification of PVCs becomes particularly crucial in such scenarios due to their association with an elevated risk of sudden cardiac death (SCD) [1]. Several studies have evaluated the arrhythmic risk posed by PVCs in apparently normal hearts; however, in the majority of cases echocardiography was the sole imaging modality utilized. Only few studies have evaluated the prognostic significance of advanced imaging techniques like CMR in this setting of patients [15,16]. Thus, the aim of our systematic review was to provide, for the first time, an exhaustive insight on the prevalence of concealed SHD detected by CMR, along with any associated high-risk clinical and electrocardiographic features, in patients exhibiting high burden of PVCs despite an apparently healthy cardiac findings on echocardiography.

2. Materials and methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement, aiming to explore the role of CMR in detecting concealed SHD among patients presenting with PVCs and absence of cardiac anomalies during echocardiographic assessment [17]. The review process encompassed comprehensive literature search, study selection, eligibility criteria, data extraction, and quality assessment, all of which were independently conducted by two reviewers, namely P.B. and N.S. Any disagreements were resolved through discussion and consensus or adjudication from a third author (A.I.G). The review process and the search strings for each database are provided in the Supplementary materials. The outcomes of identification, screening, eligibility assessment, and inclusion are outlined in the PRISMA flow diagram (Supplementary Figure).

3. Results

3.1. Included studies

A total of 17 published studies spanning from 1997 to 2023 were selected and included in the systematic review [18–34] (Supplementary Table). No relevant risk of bias was detected in any of the selected studies. All studies exhibited an observational design, with two of them being multicentric. About 94% of studies (16 cases) enrolled adult subjects without positive personal history of SHD and with negative routine diagnostic workup. Six studies focused on specific populations, including athletes in five studies and children /adolescents in one study. Participant ages varied across studies, with a prevalence of young and middle-aged subjects. The highest median age (62 years old) was observed in the study of Scorza et al. [32]. Regarding sex distribution, a wide range was observed, with proportion ranging from 49% to 85% of male individuals across studies [21,23], indicating an overall prevalence of male sex across studies.

3.2. Clinical evaluation

Some studies reported that male sex and older age were independent predictors of abnormal CMR findings [27,28]. These observations were further supported by a recent analysis of a large multicenter international registry, which revealed that male sex (Odds Ratio (OR): 4.28, 95% Confidence Interval (CI): [2.06,8.93], $p = 0.01$) and a family history of SCD and/or cardiomyopathies (OR: 3.61, 95% CI: [1.33, 9.82], p = 0.01) were significantly associated with the presence of myocardial abnormalities on CMR evaluation [26].

3.3. Electrocardiography

Certain characteristics such as T wave inversion on resting EKG (OR: 5.2, 95% CI: [1.0,27.1], $p = 0.05$) and/or complex VAs (OR: 4.5, 95% CI: [1.1, 18.7], $p = 0.04$) were associated with abnormal CMR outcomes at multivariable analysis [24]. Additionally, PVCs with a RBBB and intermediate or superior axis represent an independent predictor of left ventricular (LV) LGE on CMR [23,25,28]. On the contrary, the contemporary presence of qR pattern in lead aVR and V1 with RBBB and superior/intermediate axis, or a relatively narrow QRS with an intermediate axis, was associated with the absence of LGE [23]. The complexity of VAs is another important factor; particularly, sustained ventricular tachycardias (VTs) were identified as significant predictors of SHD at multivariate analysis (OR: 2.23, 95% CI:[1.26, 3.92], $p < 0.001$) [18]. Reproducibility of VAs during a repeated exercise test (ET) emerged as another important risk feature, potentially indicating a higher risk of non-ischemic left ventricular scar (NILVS) in athletes [21]. However, some studies have reported no significant relationship between CMR abnormalities and PVCs morphology during exercise [33].

3.4. CMR imaging

The identification of a concealed SHD on CMR varies substantially across studies, ranging from a lower percentage (11% of cases) observed in the study of Crescenzi et al. among young athletes, to a notably higher prevalence (84% of patients) reported in the study of Proclemer et al. [25,30]. CMR findings in a relevant percentage of cases was compatible with history of myocarditis, which may manifest without overt symptoms [18,27], followed by arrhythmogenic cardiomyopathies, with the identification of myocardial fatty replacement and/or regional wall motion abnormalities [28,33]. Dilated cardiomyopathy, ischemic heart disease, hypertrophic cardiomyopathy and congenital heart disease were also reported; however, in a non-negligible percentage of cases, CMR findings may be non-specific, thereby posing challenges in achieving a definite diagnosis [18].

3.5. Prognostic implications of CMR findings

CMR with LGE sequences was able to identify the presence of myocardial fibrosis. Two studies reported that the most common localizations were within the LV inferolateral, inferior, and anterolateral walls, frequently exhibiting mid-myocardial and/or subepicardial involvement [26,28].

The identification of LGE on CMR may have important prognostic implications. However, only five studies from our cohort reported a follow up of patients who underwent CMR. In the study of Sestito and colleagues, no serious events were observed in all enrolled subjects, despite a high percentage (74%) of concealed SHD, albeit not evaluated with LGE [33]. Similarly, Andreini et al. reported a low rate of cardiovascular events during a follow-up period of 5 years, despite the identification of LGE in about half of the patients with SHD [18].

Conversely, other studies reported contrasting results: Nucifora et al. observed that myocardial structural abnormalities were associated with worse outcomes [Hazard Ratio (HR): 41.6 95% CI:[5.2, 225.0], $p < 0.001$] [28]. Aquaro et al. reported higher incidence of adverse cardiovascular events in patients with PVCs of LBBB morphology and right ventricular (RV) abnormalities detected with CMR during a follow-up period of approximately 4 years [19]. Particularly remarkable findings were presented by the multicentric study of Muser et al., which revealed that the presence of myocardial abnormalities on CMR was associated with a higher incidence of serious arrhythmic events compared to patients with normal CMR findings (29% vs 0.2%, $p < 0.01$) after a follow

up period of approximately 5 years [26].

3.6. Role of CMR in athletes

The significance of identifying concealed SHD is particularly heightened in athletes. Our analysis highlights a considerable prevalence of cardiac fibrosis detected by CMR with LGE evaluation in this population, ranging from 11% to 44% [21,23–25,34].

The morphology, complexity, and response to ET of PVCs are crucial features predictive of CMR abnormalities. In a multivariable analysis involving a large athlete population, important predictors of LGE included the presence of PVCs with a RBBB and intermediate/superior axis morphology, as well as the onset of polymorphic VAs during the ET. On the contrary, LGE was absent in subjects with a LBBB configuration and inferior axis (infundibular pattern) [25]. Similarly, Calò et al. observed a high rate (29%) of LGE at CMR in 121 athletes with a monomorphic PVCs and a RBBB intermediate/superior axis morphology, whereas total absence of LGE was observed in cases with a consensual qR pattern in leads aVR and V1 or a narrow QRS with intermediate axis [23].

4. Discussion

The identification of frequent PVCs on surface EKG is not rare during a clinical evaluation [1]. Their presence should be considered as a potential marker of SHD necessitating further diagnostic investigations (Fig. 1).

Surface 12-leads EKG and 24-h dynamic EKG are essential to assess the morphology, frequency, and complexity of PVCs. A wide QRS with left bundle branch block (LBBB) and inferior axis is typical of right ventricular outflow tract (RVOT) VAs, a usually benign condition with a structurally normal heart [35]. Conversely, PVCs originating from the left ventricular outflow tract (LVOT) typically exhibit a right bundle branch block (RBBB)-like morphology and an inferior axis [36]. PVCs not originating from outflow tracts and displaying different morphologies are often associated with the presence of myocardial abnormalities on CMR (Fig. 2) [26,27,37]. Regarding the daily burden of PVCs, the cutoff adopted as an inclusion criterion varies extremely across studies. A rate of PVCs >1000/24 h was considered in several studies [18,19,24,27,28,32,34]. However, these studies did not find a clear relationship between the daily burden of PVCs and the prevalence of SHD, suggesting that more attention should be addressed to PVCs morphology and complexity rather than solely focusing on PVC frequency.

CMR represents an advanced non-invasive imaging modality with high accuracy in the assessment of heart chambers and myocardial tissue characterization, with relevant prognostic and therapeutic implications [2,38–41]. Consequently, the latest European Guidelines have underscored the importance of CMR for cardiomyopathies workup and management of patients with Vas. The need to exclude a SHD has reported to be particularly useful in case of inconclusive ECG and basic echocardiography [2]. In the absence of structural alterations, PVCs may be deemed idiopathic and managed with medical therapy or catheter ablation if symptomatic. However, if SHD is present, therapeutic management should focus on the treatment and follow-up of the underlying disease [2]. Atypical features such as older age, RBBB configuration, or sustained monomorphic VTs consistent with re-entry phenomenon may also suggest CMR evaluation [2]. Indeed, CMR emerges as the premier imaging modality for identifying reversible or irreversible myocardial alterations that could serve as trigger zones for VAs [42,43].

The significance of myocardial fibrosis, as assessed with LGE sequences, was explored in several studies, especially in patients with non-ischemic and ischemic dilated cardiomyopathy, suggesting its correlation with increased cardiovascular mortality and incidence of ventricular arrhythmic events [44–47]. Importantly, our data indicate a relevant prevalence of LGE, ranging from 8% to 44%, with most common localizations including the inferolateral, inferior and anterolateral walls of the LV, frequently displaying mid-myocardial and/or sub-epicardial involvement [26,28].

In general, in subjects with a normal diagnostic workup, the prevalence of concealed SHD revealed by CMR is non-negligible, ranging from 11% to 84% of cases.

Although CMR findings may often be non-specific, impeding a precise diagnosis in several instances, it was reported that these alterations

Fig. 1. A case of a young female patient complaining of palpitations.
In the panel c: a surface 12-lead EKG depicts a normal heartbeat followed by a PVC. The 24-h ambulatory EKG reveals a high burden of PVCs and a Non-Sustained Ventricular Tachycardia (NSVT). Transthoracic echocardiography (panel d-e) shows no relevant structural cardiac alterations. A further diagnostic refinement with CMR (panel a-b) highlighted a mild left ventricular dilation and the presence of LGE with subepicardial distribution in the interventricular septum and lateral wall. Subsequent genetic testing revealed a pathogenic mutation in the desmoplakin gene.
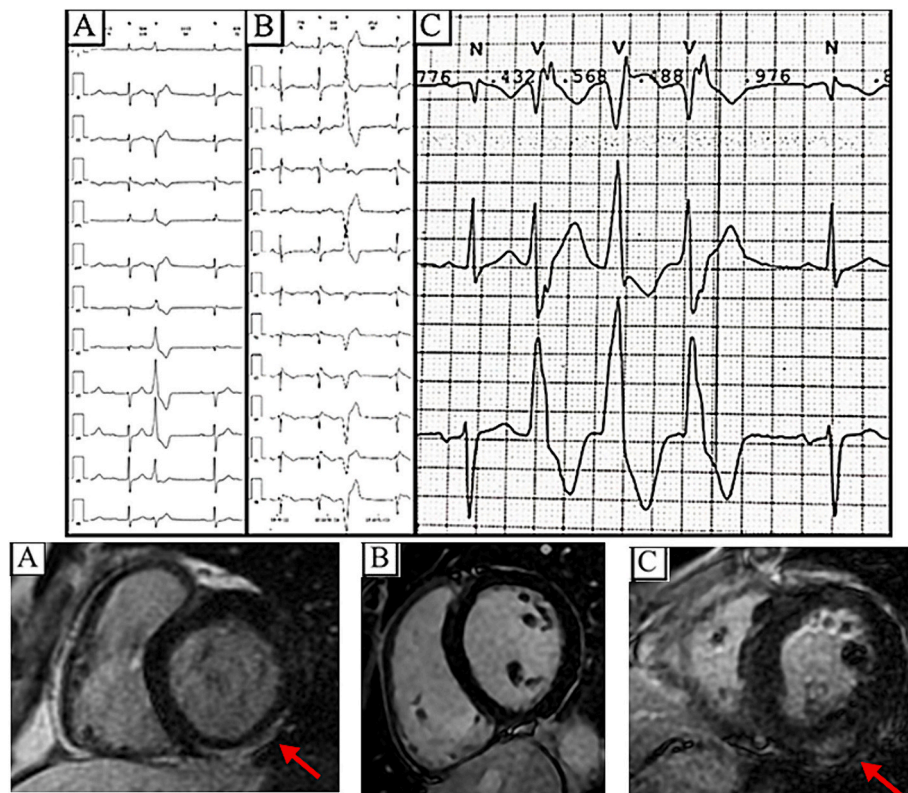
Fig. 2. Morphological characteristics of PVCs at EKG.
A) PVC with RBBB morphology and superior QRS axis, a condition representing a predictor of left ventricular LGE at CMR. The CMR displayed the presence of a subepicardial fibrosis in the posterolateral LV (arrow). B) PVC with LBBB inferior axis morphology, consistent with RVOT origin, often suggesting a benign condition, confirmed at CMR. C) NSVT, a potential predictor of SHD. In this case the CMR revealed an area of LGE in the LV (arrow).

were frequently associated with previous myocarditis or ARVC [18,22,27]. Fig. 3 summarizes the main pathological findings observed through CMR. The identification of concealed SHD in the presence of PVCs carries important prognostic implications. While some smaller studies have reported favorable outcomes, pivotal insights have been gleaned from a large multicentric registry, highlighting that concealed SHD is associated with a higher incidence of serious arrhythmic events [26].

The role of CMR may be crucial in specific populations such as young athletes. In these subjects a safety exclusion of SHD is essential to guarantee the suitability for competitive physical activities, thereby excluding the risk of life-threating arrhythmic events during sports. Previous studies reported a higher prevalence of VAs in athletes compared to non-athletic general population. Termed "athlete's heart syndrome", this phenomenon typically poses no adverse significance in the absence of cardiovascular abnormalities upon clinical and noninvasive evaluation [48]. Our analysis suggests that the prevalence of concealed SHD and LGE was relevant in this population [21,23–25,34]. Adjunctive diagnostic tests, such as ET, prove valuable for a comprehensive evaluation of PVCs characteristics. Indeed, the reproducibility of VAs during ET and exercise-induced complex VAs with a RBBB or polymorphic morphology are associated with underlying structural cardiac alterations [24].

In conclusion, through this systematic review, we sought to highlight the indispensable role of CMR as an imaging technique to reveal concealed cardiac abnormalities in a noteworthy proportion of patients with frequent PVCs, which may elude detection by clinical evaluation and conventional echocardiography in a relevant percentage of cases. When pathological CMR findings, especially those involving LGE, are present, patients may face an independent risk of harmful VAs and SCD, necessitating prompt evaluation to tailor appropriate therapy. Certain clinical characteristics, such as male sex, older age, or family history of SCD, alongside high-risk PVC features on EKG, such as complexity or RBBB and superior/intermediate axis morphology, may require a thorough diagnostic assessment with CMR (Fig. 4). In athletes, the presence of PVCs should not merely be attributed to 'athlete's heart' but often necessitates further assessment with CMR to safely exclude SHD.

CRediT authorship contribution statement

Nicolò Soldato: Writing – original draft, Investigation. **Erika Pedio:** Investigation, Formal analysis. **Paola Siena:** Writing – original draft, Conceptualization. **Maria Cristina Carella:** Writing – original draft, Methodology. **Ilaria Dentamaro:** Investigation, Data curation. **Yamna Khan:** Writing – original draft. **Andrea Baggiano:** Visualization. **Saima Mushtaq:** Visualization. **Cinzia Forleo:** Writing – review & editing. **Marco Matteo Ciccone:** Writing – review & editing. **Gianluca Pontone:** Writing – review & editing, Supervision. **Andrea Igoren Guaricci:** Supervision, Project administration, Conceptualization.

Declaration of generative AI and AI-assisted technologies in the writing process

No generative AI and AI-assisted technologies were used in the writing process for this review.
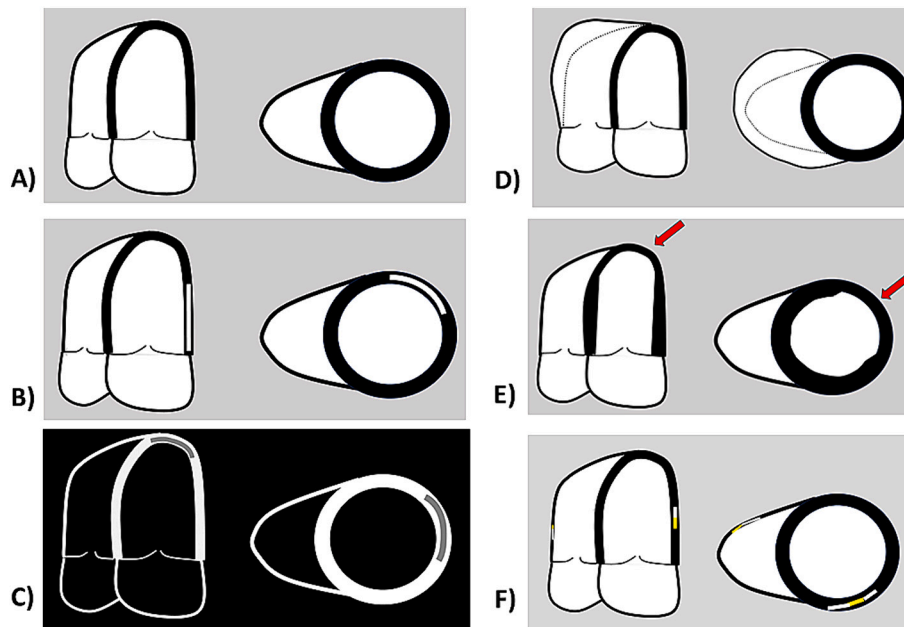
Fig. 3. Main structural findings at CMR evaluation.

In the figure are summarized the main cardiac structural cardiac alterations detected with CMR. In each panel was outlined a four-chamber view (on the left) and a short axis view (on the right) of the heart. CMR represents an advanced imaging modality with high accuracy in the morpho-functional assessment of heart chambers. Moreover, adopting dedicated sequences, it is the unique non-invasive modality able to provide a myocardial tissue characterization. A) A normal heart evaluated through the application of non-gated balanced steady-state free precession (b-SSFP) sequence. B) Myocardial fibrosis in the left ventricular wall evaluated with late gadolinium enhancement (LGE) sequences. C) A STIR T2 W (short tau inversion recovery T2 weighted) sequences displaying myocardial oedema in the left ventricle. D) Chamber dilation: the cardiac chamber's dimensions and volumes are evaluated using T1 weighted sequence. E) Segmental cardiac wall motion abnormalities: akinetic or hypokinetic areas of the myocardial wall (red arrow) may be pointed out using cine b-SSFP sequences. F) Fibrofatty replacement evaluated with black-blood imaging T1- or PD (photon density) - weighted FSE (fast spin echo). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
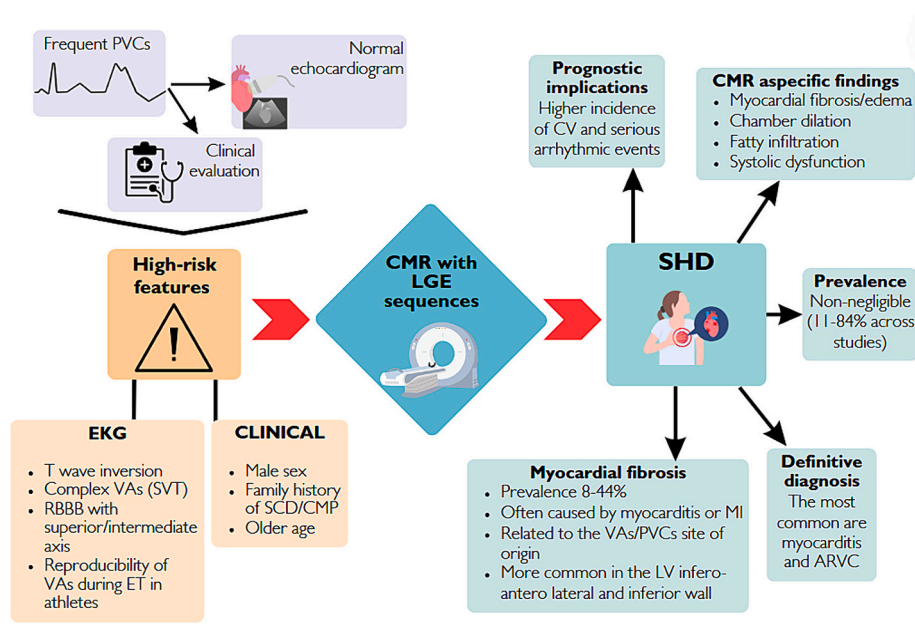

Fig. 4. The role of CMR in the evaluation of patients with frequent PVCs.

When frequent PVCs are observed on surface 12-lead EKG or 24-h dynamic EKG, the first-line imaging tool is echocardiography. In presence of specific clinical and EKG high risk-features, CMR with LGE sequences may detect SHD with relevant therapeutic and prognostic implications.

Declaration of competing interest

The authors have no relevant financial and non-financial interests to disclose.

Data availability

No new data were created for this review.

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