



Arrhythmia-induced Cardiomyopathy: An Article Review

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Abstract

Arrhythmia is one of the significant reversible causes in patients with heart disease and left ventricular dysfunction. Tachycardia, atrial fibrillation, and premature ventricular contractions have indeed been related to arrhythmia-induced cardiomyopathy (CM), a reversible dilated CM. Effective arrhythmia suppression will entirely or partially recover ventricular function, lowering morbidity and mortality. However, the importance of arrhythmia-induced CM (ARiCM) is often underestimated in clinical practice because arrhythmia is often seen as a result rather than a cause of CM, leading in treatment delays and failure to increase the quality of life and better clinical outcomes. This article review aims to summarize the pathomechanisms, and a general approach to the management of ARiCM and its long-term outcomes. ARiCM can cause a variety of clinical signs, ranging from asymptomatic to severe heart failure symptoms. Electrocardiogram, 24 h Holter monitoring, echocardiography, and cardiac magnetic resonance are all recommended for diagnosis. More research is required to better understand the pathogenesis of ARiCM and to differentiate treatment alternatives to choose the ideal ARiCM management approach

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Introduction

Cardiomyopathy (CM) is a disease that affects the heart muscle and results in ventricular enlargement and systolic dysfunction, in the type of dilated CM (DCM) [1]. One of the essential reversible causes is arrhythmia-induced CM (ARiCM), which is characterized by rapid or irregular ventricular rate and leads to the left ventricular (LV) systolic dysfunction (LVSD) [2]. Reversible causes are essential because the poor long-term prognosis of idiopathic dilated cardiomyopathy [1]. Therefore, treating reversible causes will totally or partially reverse CM. However, in the incidence of pre-existing systemic heart disease, ARiCM can worsen LVSD, making it only partially reversible [2].

Tachyarrhythmias of various types may result in ventricular dysfunction and heart failure (HF). Atrial tachycardia (AT) is a common arrhythmia, if persistent, can lead to ARiCM. T-CMP was observed in 8.3–10% of patients in trials of focal AT in adults and 28% in children [3], [4]. What is even more remarkable is that about one-third of patients with atrial fibrillation (AF) and systolic HF consequently have LVSD predominantly, with ARiCM observed in 58–88% of cases [2].

In patients with LVSD and AF, significant improvement in ejection fraction is 58–68% after ablation, meaning that many of these patients have reversible ventricular dysfunction related to AF [5], [6]. In different studies of radiofrequency ablation (RFA) of premature ventricular complexes (PVCs), PVC-induced ventricular dysfunction discovered by 7–30% [7]. As a result of the recognition of several arrhythmias besides tachycardia as a cause of CM, the term ARiCM has developed to include tachycardia-induced CM (T-CM), PVC-induced CM (PVC-CM), and AF-induced CM (AF-CM) [8].

ARiCM has a wide variety of clinical manifestations, solely responsible for the CM (Type 1) or contributing to the underlying CM (Type 2) [9]. In Type 1 ARiCM, successful treatment can turn to complete resolutions, which LV function returns to normal. In contrast, treatment of type 2 ARiCM results in partial resolution of the CM [10]. Unfortunately, the importance of ARiCM is underestimated in clinical practice since arrhythmia is often seen as a result rather than a cause of CM, resulting in a delay of treatment [2].

In this article review, we aim to summarize the cause, pathomechanism, general approach to the management of ARiCM, and its effects, focusing on T-CM, PVC-CM, and AF-CM (Figure 1).

	T-CM	PVC-CM	AF-CM
Cause	Chronic Elevate HR	Heart rate irregularity	Elevated HR
		Genetic	Lack of atrial systolic activity
		Dyssynchrony AV Dyssynchrony	Genetic
		Postextrasystolic Potentiation	
		Sympathetic Activation	
Patomechanism	Alternations at myocyte and myocardium level: myocyte misalignment → biventricular dilatation	Abnormalities of the calcium-induced calcium release pathway and changes in dyad activity → contractile dysfunction	Coordinated atrial contraction: Reduction cardiac output, and atrial contraction affects the cardiac output
	Electrical remodelling and pathological Ca homeostasis: impaired excitation-contraction coupling and diastolic dysfunction	Histopathological findings: Minimal/ no fibrosis without an elevated inflammation/ apoptosis	Genetic mutations: Impaired contractile function, cellular integrity, and/or cytoskeletal structure
	Time-dependent ventricular remodeling	Electrophysiological remodeling	
		Genetic R222Q missense: rate-dependent ectopy purkinje correlated with CM	
Therapy	Ablation or antiarrhythmic drug		
Effect	Normalized LVEF	Normalized LVEF	Normalized LVEF
	LV mass rises by 26%	Possible cause for recurrent PVC-CM: Myocarditis	
	LV remains dilated		
	Fibrosis continue to exist		
	Rapid reduction in pro-BNP		
	Myocytes continue to exhibit contractile dysfunction		

Figure 1: Summary pathomechanism of ARiCM. T-CM: Tachycardia-induced cardiomyopathy, PVC-CM: Premature ventricular complex-induced cardiomyopathy, AF-CM: Atrial fibrillation-induced cardiomyopathy, HR: Heart rate, AV: Atrioventricular, LV: Left ventricular, LVEF: Left ventricular ejection fraction

Tachycardia-induced CM

Definition and prevalence

T-CM is a type of reversible myocardial dysfunction induced by persistent arrhythmias that have been observed in experimental animals as well as in individuals with supraventricular and ventricular tachyarrhythmias [3]. Gossage *et al.* first described T-CMP in a patient with AF and rapid ventricular response in 1913. Following that, in an animal model,

the development of reversible HF with rapid pacing was demonstrated. T-CMP was then coined to describe the development of ventricular dysfunction as a result of rapid ventricular rate, regardless of the type of tachycardia [1].

T-CM shows the presence of reversible LV dysfunction caused only by an increase in ventricular rates. The risk of developing T-CM is determined by the type of tachycardia and the tachycardia's rate and duration. T-CM has been confirmed to appear weeks, months, or years after the onset of tachycardia [8].

T-CM has been documented in 10% of patients with AT and 37% of patients with persistent AT. Furthermore, the highest correlation with T-CM was found in permanent junctional reciprocating tachycardia in up to 50% since it often manifests as a persistent supraventricular tachycardia (SVT) [11]. In up to 25% of cases, atrial flutter is associated with LV dysfunction, with most cases increasing their LV function following cessation of the arrhythmia [12]. In addition, a 96% complete full recovery of LV function was discovered from a successful catheter ablation in 25–30 patients with T-CM [10].

Mechanism and pathophysiology

Understanding the pathomechanism of T-CM has relied on animal models. Animals exposed to chronic tachycardia using continuous pacing develop HF manifestations, LVSD, and LV biventricular dilatation, reduction in myocardial blood flow, as well as a rise in LV wall stress, end-diastolic pressure, and volume [13]. All animal models demonstrated time-dependent ventricular remodeling in association with the development of HF. These physiological changes will progress, which include a 1 week plateau of decrease in systemic blood pressure, LV, and pulmonary artery pressure, while cardiac output, ejection fraction, and volumes begin to decline over the next 4 weeks, with the onset of symptomatic HF occurring within 2–3 weeks [14].

Chronic rapid pacing also causes alterations at the myocyte and myocardium levels. The main changes observed are depletion of myocyte energy, mitochondrial dysfunctions with increased oxidative enzymes, myocyte elongations, reduced myocyte attachment with the basement membrane, activations of proapoptotic cascades, and myocyte loss. There is also a significant depletion of the extracellular matrix. This weakens myocyte support and induces myocytes' misalignment, leading to biventricular dilatation with no improvement or ventricular wall thinning [1], [15], [16]. Electrical remodeling and pathological Ca homeostasis have also been observed in T-CM models, which are believed to be responsible for impaired excitation-contraction coupling and diastolic dysfunction [13], [17]. The only total Ca cycling, Ca channel inhibition, and basal ATPase activity have shown a statistically relevant association with a decrease in the LV ejection fraction (LVEF) [16].

As tachycardia pacing is stopped, the right atrial and arterial pressures normalize, with substantial improvement of the LVEF and cardiac activity within 48 h and total normalization within 1–2 weeks [13]. However, after a week, when tachycardia is resolved, 26% of LV mass raised, the LV still dilated, and myocytes remain to exhibit contractile dysfunction [8]. Furthermore, despite the normalization of the LV function, specific changes, such as fibrosis, continue to exist [17].

Clinical Presentation and Diagnosis

Clinical trials have discovered a variable time between the onset of arrhythmia signs and T-CM development, varying from 3 until 120 days with an average LVEF is 32% [18]. Regardless of tachyarrhythmia, symptoms of HF occur earlier in patients with higher rates of tachycardia [14], [17], such as those with persistent atrial flutter or tachycardia with 2:1 atrioventricular (AV) conduction at rates of 150 beats/min. A latest clinical research discovered that T-CM had more serious LV dysfunction than dilated and inflammatory CM [19].

Palpitations are the most often reported symptoms, followed by HF Class III to IV and syncope/pre-syncope, with the remaining showing no symptoms [20]. While sudden cardiac death is rare, it has been confirmed in up to 8–12% of cases after treatment and CM resolution [18], [21]. However, T-CM can appear as persistent or paroxysmal tachycardia, and it should be expected in patients with the LV dysfunction and a previous, chronic, or recurrent paroxysmal tachycardia with no obvious etiology. If the tachycardia is present, despite underlying secondary CM, a superimposed T-CM should be considered. Therefore, an ambulatory electrocardiogram (ECG) monitor is critical to validate or exclude T-CM for at least 2 weeks [18], [22].

Other etiologies can be ruled out with the aid of an echocardiogram and cardiac magnetic resonance imaging. T-CM is distinguished by DCM, moderate-to-severe biventricular systolic dysfunction, and normal LV septal and posterior wall thickness [17]. Natriuretic peptide (BNP) and pro-BNP are often elevated in heart disease and CM patients [16], [18]. Furthermore, a rapid reduction in pro-BNP within a week of tachycardia elimination supports T-CM [16].

However, T-CM's definitive diagnosis can only be confirmed after regeneration of LV systolic function within 1–6 months of tachyarrhythmia elimination [22]. Although no preliminary imaging or biochemical measurement can conclusively differentiate ARiCMP from other kinds of non-ischemic DCM, numerous indicators have been discovered that assist to predict considerable LV functional recovery after optimal arrhythmia management [23].

A recent research examined on endomyocardial biopsies from 189 people with non-ischemic new-onset HF, 19 of whom were classified as ARiCMP retrospectively. The ARiCMP cases were compared to 91 patients with inflammatory CM and 79 individuals with DCM. The researchers observed that ARiCMP patients' LV biopsies exhibited greater levels of major histocompatibility complex Class II expression and more CD68 macrophage infiltration than DCM. Mitochondria were disproportionately distributed toward the intercalated disks in compared to healthy individuals. Myocardial fibrosis was also identified in ARiCMP,

however, it was less severe than in inflammatory CM and DCM [19].

Furthermore, ARiCMP patients had smaller LV cavities than DCM patients with accompanying arrhythmia. ARiCMP is also indicated by early right ventricular systolic failure on MRI. A recent study showed the utilization of longitudinal strain (LS) by echocardiographic speckle tracking in predicting LV functional recovery in clinically suspected ARiCMP patients. Patients with ARiCMP exhibited a more substantial reduction in apical LS compared to the mid and basal segments at baseline, whereas patients with persisting LV dysfunction after arrhythmia treatment had a greater reduction in LS in the basal segments [23].

PVC-CM

Definition and prevalence

PVCs were assumed to be benign. However, CM caused by recurrent PVCs in otherwise healthy cardiac has been observed in the recent decade [24]. Although PVC-CM was initially described as T-CMP, they did not have prolonged tachycardia, and distinct pathomechanisms might contribute to ventricular dysfunction [1]. As a result, the latest 2016 AHA Research Statement on dilated cardiomyopathies acknowledges PVC-CM as a separate clinical classification. PVC-CM is characterized as the development of LV dysfunction independently as a result of frequent PVCs. In living humans, PVC-CM is defined by an enhancement in LVEF following PVC therapy or by the solely presence of PVCs in a structurally normal heart and later LV dysfunction [17]. Furthermore, superimposed PVC-CM is characterized as an increase in LVEF of at least 10% due to frequent PVCs in a previously established CM [18].

The prevalence of ARiCM in PVCs patients has been estimated to range in 9–34% [9]. The prevalence of PVCs in ECG is reported between 1% and 4% in patients without heart disease. On the other hand, the prevalence of PVCs is considerably higher during ambulatory ECG recording [25]. The wide variations of PVCs frequency can demonstrate this over time. PVC incidence ranges with age, varying from 1% in children under 11 to approximately 70% in subjects 75 and older. PVCs were often linked with HF, DCM, coronary heart disease, and post-myocardial infarction [26].

Mechanism and pathophysiology

In the presence of frequent PVCs, ARiCM development is multifactorial. Heart rate irregularity, pre- and intraventricular dyssynchrony, AV dyssynchrony, post-extrasystolic potentiation, and sympathetic activation are the major suggested mechanisms [27]. The

predominant cause of PVC-CM contractile dysfunction tends to be abnormalities of the calcium-induced calcium release pathway, with changes in dyad activity are suggested as a possible mechanism [22].

Similar to other cardiomyopathies, electrophysiological remodeling found in PVC-CM. However, different histopathology abnormalities also found with minimal or no fibrosis without an elevated inflammation or apoptosis. Mitochondrial analysis has revealed no improvements in phosphorylation oxidative. These results are scientifically confirmed by the absence of scar on cardiac magnetic resonance imaging in patients with PVC-CM [28]. These results also support the hypothesis that primary cause of this reversible CM is a primary functional abnormality. It is unknown if any cellular and molecular modifications result from CM or the CM's source [22]. Finally, genetic cause, particularly R222Q, can explain why some patients develop PVC-CM while others do not, despite having a similar PVC burden [29].

Clinical Presentation and Diagnosis

The time window for PVC-CM development is unknown, although it is expected to take months to several years [30]. While animal experiments with persistently high PVC burdens (33–50%) grow CM within 4 weeks, human studies are inconsistent because of uncertain onset and variant of PVCs [22]. PVC-CM may present with various symptoms, ranging from unclear symptoms to HF and even syncope [31]. A thorough history and relevant tests such as echocardiography, ECG, and 24 h Holter monitoring, and cardiac magnetic resonance should be done to rule out other CM causes, while the physical examination is usually normal, except for abnormal heart sounds and signs of HF [22]. The absolute number of PVCs per day and the total burden of PVC-induced CM are negatively linked to LVEF and directly related to measurements of LV end-diastolic volume [23].

PVC-CM is an exclusion diagnosis that should be considered in patients with recurrent PVCs >10% of the time, particularly in non-ischemic CM. The difficulty is determining whether PVCs are the cause of CM or not in patients with CM. Even if CM causes PVCs, if they occur often, they can lead to and exacerbate CM and HF symptoms; referred to as “superimposed” PVC-CM [32]. In certain cases, echocardiographic and PVC features may aid in the identification of these patients. An echocardiogram should be repeated to validate a normal LV function [22].

Despite the ECG's importance, a continuous ambulatory ECG monitor is needed to boost the high PVC burden's diagnostic yield. A study reported that detecting an individual's full PVC pressure requires at least 6 days. In comparison, a 24 h Holter found only

53% of patients with a PVC burden >10%, implying that almost half of patients with possible PVC-CM diagnosis were missed [24]. Another study introduced a PVC burden of 13% as the optimal cutoff for estimating LV recovery with 100% sensitivity and 85% precision of independent of coexisting systemic heart disease [33].

PVC-CM is distinguished by mild-to-severe LVSD, LV dilatation, mild mitral regurgitation, and left atrial (LA) enlargement that resolves in 2–12 weeks after eliminating PVCs. Cardiac imaging is critical for detecting LV dysfunction and raising the suspicion of PVC-CM in patients with a high PVC burden (>10%) [34]. Cardiac magnetic resonance with late gadolinium enhancement provides the benefit of detecting and measuring scar burden, which may predict the response to PVC control [22].

Recently, myocarditis has been identified as a possible cause for recurrent PVCs and CM, and elevated hs-CRP has been identified as an independent indicator of PVCs in a Chinese population sample [35].

Atrial Fibrillation-Induced CM

Definition and prevalence

While AF can induce CM because of the rapid ventricular rate, it was discovered that ventricular dysfunction may also present in patients with AF who had a controlled ventricular rate. As a consequence, the term AF-induced CM was introduced [22]. AF is the most common cause of ARiCM in adults. AF and HF are modern epidemics that often coexist and predispose to one another. Patients with AF have a greater chance in the development of HF in the Framingham report [36].

AF-CM is characterized as LV systolic dysfunction in patients with paroxysmal or persistent AF despite adequate rate control. As a result, an ambulatory Holter monitor is essential for ruling out inadequate rate control and T-CM. A common clinical challenge is determining whether the AF is caused by HF and CM or conversely [22].

Mechanism and Pathophysiology

Tachycardia, elevated heart rhythm, lack of atrial systolic activity, and genetic causes are among the pathomechanism processes causing the progression or worsen CM in AF patients. The irregular contraction has negative hemodynamic effects that are unrelated to heart rate [37], [38]. The following factors are also thought to contribute to AF-CM. Irregular heart rate associated with calcium mishandling and

loss of atrial contraction associated with sympathetic activation, which contributes to restricted ventricular filling and elevated filling pressures, functional mitral regurgitation, and diastolic dysfunction. Unfortunately, there are no AF-CM animal models available to help researchers better grasp the etiology causation, risk factors, or mechanism [22].

In patients with controlled AF and LV dysfunction, the LV function improved after AV nodal ablation, which regularizes ventricular rhythm with pacing [37], [38]. Coordinated atrial contraction in AF contributes 20% of cardiac output and atrial contraction reduction which affects the cardiac output [10], [37].

Aside from rapid ventricular rates, ventricular rate irregularity itself can have negative hemodynamic implications, leading to the LV dysfunction [39]. Moreover, non-ischemic CM has been linked to various genetic mutations structure and contractile function [40]. Over 50 genes have been related to DCM, and they can be present in up to 30% of patients [41].

Clinical Manifestation and Diagnosis

AF-CM is an exclusion diagnosis that should be considered in individuals with persistent AF and non-ischemic CM who do not improve after sufficient medical therapy and rate monitoring. Furthermore, it is uncertain if the time frame or imaging characteristics of AF-CM and T-CM differ, because of the similarities with T-CM and the absence of animal models. Therefore, AF-CM diagnosis will only be confirmed if the LV systolic function improves after AF elimination [22].

Since AF in the setting of HF could be present at the time of the first contact, the initial target should be rate control using beta-blockers digitalis and drug treatment for HF. At the moment, a resting heart rate of 60–100 beats/min and light exercise heart rate of <110 beats/min are advised [2], [42].

General Treatment of ARiCM

Since arrhythmia suppression will totally or partly reverse ventricular dysfunction in ARiCM, the critical component of management is successful arrhythmia suppression with antiarrhythmic drugs (AADs) or RFA [1]. The strategy used to manage arrhythmia is determined by the degree of arrhythmia, the patient's status, and any known comorbidities. T-CM reversibility is significant after tachycardia is eliminated. However, T-CM's initial treatment should include initiating and optimizing medical treatment for HF and LVSD to

optimize reverse remodeling. Unfortunately, despite normalization of LVEF, histopathological abnormalities, ventricular dilatation with hypertrophic reaction and diastolic dysfunction, may persist [8], [17], [19]. However, treatment should not be discouraged since it can have significant benefits [22].

RFA has a high success record in treating arrhythmias. If the patient's condition worsens despite adequate rate control, the target should be establishing sinus rhythm. While AADs have a lower success rate ranging from 35% to 70% in establishing sinus rhythm, with recurrent adverse effects, AF ablation has shown a higher success rate ranging from 70% to 90% and fewer adverse effects [6]. Furthermore, one randomized clinical trial has closely compared amiodarone and AF ablation for rhythm control in AF and HF patients. After 2 years, ablation (70%) was shown to be superior to amiodarone (34%) in terms of establishing sinus rhythm, with less hospitalization and mortality [43].

PVC suppression is deemed effective when PVC strain decreases by more than 80%. In multiple trials, both AADs and RFA demonstrated long-term performance rates ranging from 70% to 80%. Beta-blockers are the most prevalently prescribed AAD for frequent PVCs because of its lack of significant side effects. Other AADs, such as amiodarone, dofetilide, sotalol, mexiletine, or flecainide, may be more effective than beta-blockers, but they are associated with severe side effects and a risk of pro-arrhythmia. Because of the elevated mortality found in the CAST study, the current guidelines should not recommend their use [44]. A recent retrospective analysis found that flecainide and propafenone were effective in PVC-CM without raising mortality or ventricular arrhythmia [1]. There is no randomized controlled trial comparing RFA and AADs for PVC suppression, although a one study showed that RFA is more effective than AADs [45]. However, RFA may have slight improvement or may not be possible when PVCs arise from the papillary muscles, epicardium, conduction system, or near the coronaries [1].

Prognosis and Long-Term Outcome of ARiCM

Following successful therapy, the LV function usually improved within a few weeks to months [46]. Initial outpatient follow-up every 1–3 month should be a routine and should include ECG, ECG Holter monitoring, and an echocardiogram [2]. Depending on the inducing arrhythmia, and despite largely effective catheter ablation, arrhythmia recurrence may occur at a rate range between around 5% in SVT to nearly 50% in AF [47]. The recurrence rate of ARiCM after initial effective therapy has not been conclusively determined: A research of 12 patients (observation duration of

53 24 months) estimated it to be around 25%, and the risk of recurrence of HF occurred when the heart rate was more than 80 beats/min [48].

According to the current view, if the LV function recovers during arrhythmia therapy, the prognosis for survival is good [5]. Even after a recurrence of arrhythmia, studies have shown a rapid progression of ventricular instability and HF. This progression may be attributed to chronic histopathological abnormalities. Thus, for the treatment of ARiCM, a medication choice with a high efficacy or cure rate should be considered, and recurrences should be monitored [1].

Conclusion

ARiCM, a reversible CM, manifests in a wide range of clinical manifestation, from asymptomatic to severe HF symptoms. To diagnose this condition, the clinician must preserve a high level of suspicion. Diagnosis requires ECG, 24 h Holter monitoring, echocardiography, and cardiac magnetic resonance. An adequate diagnosis and treatment of ARiCM will improve LV dysfunction and its related complications, mortality, and health-care costs and support quality of life and long-term prognosis. More study is needed to enhance our understanding of the pathophysiology and to compare therapy options to select the suitable strategy for managing ARiCM.

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