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REVIEW

Emerging concepts in heart failure management and treatment: focus on tachycardia-induced cardiomyopathy

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Abstract

Tachycardia-induced cardiomyopathy is an entity characterized by reversible dysfunction of the left ventricle, which can be induced by different types of arrhythmia such as atrial fibrillation, atrial flutter, incessant supraventricular tachycardia and ventricular arrhythmia (more frequent causes). Correct identification of the causative arrhythmia and normalization of the heart rate (e.g through medical treatment, electrical cardioversion, ablation) can lead to recovery of left ventricular function. Tachycardia-induced cardiomyopathy should be suspected in patients with tachycardia and left ventricular dysfunction (heart failure setting), especially when there is no history of previous heart disease. Its usual phenotype is that of non-ischaemic/non-valvular dilated cardiomyopathy and it can occur in both children (main cause: permanent junctional reciprocating tachycardia) and adults (main cause: atrial fibrillation). With proper treatment, most cases recover within a few months, though there is a risk of relapse, especially when the causal arrhythmia reappears or its control is lost. This is a narrative review that comprehensively addresses the pathophysiology, clinical manifestations, and therapeutic management of tachycardia-induced cardiomyopathy.

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Introduction

The presence of a permanent or persistent tachyarrhythmia can cause generally reversible left ventricular (LV) dysfunction as an expression of a particular form of dilated cardiomyopathy, known as tachycardia-induced cardiomyopathy (TCMP).[1,2] This entity is characterized by the progressive deterioration of LV function and the subsequent development of heart failure (HF) secondary to the continuous increase in supraventricular or ventricular rates.[3]

The cessation of these arrhythmias and, therefore, normalization of the heart rate (HR) results in the recovery of myocardial function following a close cause–effect relationship that has been documented in several studies (animal and human)[3,4] and which was first described by Phillips and Levine in a patient with atrial fibrillation (AF) and reversible HF in 1949.[5] TCMP can be induced by various forms of tachyarrhythmia (Box 1), but the main forms are AF, atrial flutter, incessant supraventricular tachycardia and ventricular arrhythmias such as frequent premature ventricular complexes (PVCs).[6] On the other hand, this entity can be present in all stages of life (children, adults, and even pregnant women)[7–9] and, in this context, it is difficult to determine its real incidence and prevalence, making TCMP an underestimated condition in practice.[3,6]

Box 1. Described tachyarrhythmias associated with tachycardia-induced cardiomyopathy.

Type of arrhythmia
- Supraventricular
  - Atrial fibrillation/flutter
  - Atrial tachycardia
  - Permanent junctional reciprocating tachycardia
  - Atrioventricular nodal re-entry tachycardia
  - Atrioventricular re-entrant tachycardia
  - Inappropriate sinus tachycardia
- Ventricular
  - Ventricular outflow tract tachycardia
  - Ventricular tachycardia
  - Fascicular tachycardia
  - Bundle branch re-entry ventricular tachycardia
  - Premature ventricular complexes
- Pacing
  - Persistent rapid ventricular pacing
  - High-rate pacing

Adapted from Gupta et al.[35]

This narrative review discusses current and general aspects regarding the pathophysiology, clinical presentation, diagnostic approach, and therapeutic management of TCMP.

Review

TCMP epidemiology

TCMP has a variable incidence and prevalence depending on its causing tachyarrhythmia;[3,6] for example, it has been documented in 10% of patients with atrial tachycardia (AT),[10,11] 20–50% of patients with incessant AT,[12,13] 25% of patients with atrial flutter,[14] and in up to 50% of patients with AF.[15] AF is the most important cause of TCMP in adults[16] whilst AT and permanent junctional reciprocating tachycardia are so in children.[17]

It is generally considered that tachyarrhythmias of higher frequency and duration would induce more severe forms of cardiomyopathy[2,6] and, in this context, it is estimated that heart rates of ~110–120 bpm would be enough to develop cardiomyopathy.[18,19]

Pathophysiology

Animal models based on chronic rapid pacing have shown that LV remodelling and the development of HF is expected over time[4] just as it occurs in humans.[2,3] In this scenario, TCMP is considered to be based on a rapidly progressive remodelling process mainly related to neurohormonal activation, intracellular calcium handling defects, and extracellular matrix alterations[6] (Figure 1).

It was shown that chronic rapid pacing is followed by an early dilatation of the LV, an increase of filling pressures[20,21] and a series of common pathophysiological factors in the development of HF such as neurohormonal activation (renin–angiotensin–aldosterone and sympathetic nervous systems),[22,23] natriuretic peptide release, and the secretion of pro-inflammatory cytokines (e.g. endothelins, TNF).[22–25] In addition, the asynchronous cardiac contractions present in both AF and frequent PVCs, regardless of the greater or lesser rapidity of the heart rate, can cause excessive neurohumoral activation and, consequently, fibrosis that contributes to the development of TCMP.[1,2,6]

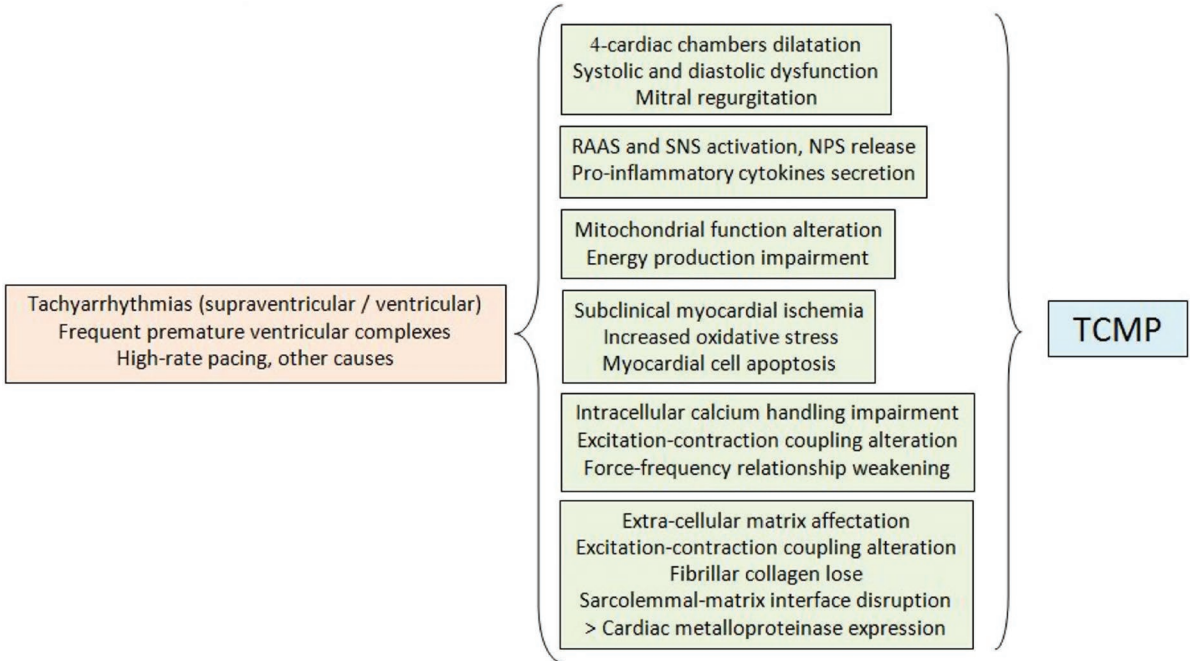
TCMP development is also accompanied by a reduction in the amplitude of the action potential and a disturbance of intracellular calcium homeostasis that impairs the force–frequency relationship, excitation–contraction coupling, and the contractile response.[26–28] Finally, the extracellular matrix is also compromised in terms of fibrillar collagen loss and disruption of the sarcolemmal–matrix interface, resulting in altered support and alignment of myocardial cells in the ventricular wall.[29–31] Other functional alterations have been described, including subclinical myocardial ischaemia, an impaired mitochondrial activity, an increased oxidative stress and myocyte apoptosis.[4,32,33] TCMP is characterized by a marked dilatation of the four cardiac chambers without hypertrophy of their walls, deterioration of systolic and diastolic function, elevation of filling pressures, and the usual presence of at least moderate functional mitral regurgitation.[2,3]

Clinical presentation and diagnosis

Once TCMP develops, its symptoms and signs are common and typical of HF (both in children and adults) in a context of higher heart rate and regardless of its aetiology; therefore, a proper timely diagnosis is important given the potential for recovery with appropriate treatment.[1,2] TCMP should be considered for any new diagnosis of LV dysfunction or HF when there is evidence of any form of frequent or persistent tachycardia or frequent PVCs.[1,2]

It has been suggested that chronic tachycardia that affects >10–15% of the day can result in cardiomyopathy and, as mentioned, HRs above 110 bpm could cause cardiomyopathy.[18,19] However, in the case of AF, asynchronous myocardial contraction also contributes[5] (such as in the case of frequent PVCs).[34] According to Gupta et al., there are elements that could indicate the presence of TCMP, especially in patients with a previous normal LV ejection fraction (LVEF), such as evidence of non-ischaemic cardiomyopathy with no other apparent

Figure 1. Pathophysiological factors involved in tachycardia-induced cardiomyopathy (TCMP) development.



Rapid chronic pacing (animal models) induce early-onset heart failure characterized by heart remodelling (four-chamber dilatation, systolic and diastolic dysfunction, and an increase of filling pressures).[20,21] Main pathophysiological alterations are related to neurohormonal overactivation, release of natriuretic peptides, secretion of pro-inflammatory cytokines and changes in the extracellular matrix. Also present (amongst others) are dysfunctions of excitation–contraction coupling and in the intracellular mitochondrial apparatus, calcium handling, and oxidative stress energy production.[22–33]
RAAS, renin–angiotensin–aldosterone system; SNS, sympathetic nervous system; NPS, natriuretic peptides system.

cause (e.g. hypertension, alcohol or drug use); absence of LV hypertrophy with a relatively preserved LV end-diastolic diameter (<5.5 cm); recovery of the LVEF after effective control of HR through medical treatment, electrical cardioversion, or radiofrequency ablation; and rapid LVEF deterioration after tachycardia recurrence in a patient with a previously recovered TCMP.[35]

According to Fenelon et al., TCMP could be divided into two subgroups: (1) pure, when tachycardia is the only mechanism of impaired LV function; and (2) impure, when there are other associated causes of LV dysfunction (most common presentation). Patients with the pure form usually have a better functional class, fewer signs of HF and more frequent palpitations. Their electrocardiogram rarely shows Q waves or signs of LV hypertrophy, whilst LV diastolic diameter tends not to be excessively dilated with a preserved parietal thickness (echocardiography).[36] On the other hand, patients with the impure type regularly present symptoms typical of HF earlier and more severely and, though clinical recovery may be relatively rapid, that of LVEF is not.[36] As mentioned, multiple rhythm disturbances can cause TCMP (Box 1) but, unfortunately, TCMP does not have any complementary tests or specific diagnostic biomarkers or algorithms that favour its identification.[1,2] Therefore, its presence should be suspected in any patient with a deteriorated LVEF and chronic or frequently recurrent tachyarrhythmia.[1,2]

Although experimentally (pacing) the development of this entity is fast (a few weeks),[4] in clinical practice, it can take from a few months to years.[1,2] Amongst other factors, the evidence of previously normal LVEF is particularly suggestive of this condition as well as a rapid drop of natriuretic peptide levels after HR control.[6] The usual imaging techniques (echocardiography or cardiac magnetic resonance) reveal the presence of dilated cardiomyopathy with moderate to severe impaired LVEF, absence of myocardial hypertrophy and functional mitral regurgitation.[1,36,37] Holter monitoring for 24 hours (or even longer) may be useful in diagnosing frequent paroxysmal cases of tachycardiomyopathy or in checking for a sustained increase in HR.[1]

The main diagnostic challenge is differentiating TCMP from non-ischaemic dilated cardiomyopathy (DCM)[2] and, compared with this, patients with TCMP usually have (at diagnosis) a higher HR and lower LVEF but with

greater LVEF recovery during follow-up (after HR normalization).[37] On the other hand, patients with DCM tend to have wider QRS complexes, more frequent late gadolinium enhancement (cardiac magnetic resonance) and more rehospitalizations during follow-up.[38] From a histopathological and immunological perspective (right ventricular biopsies), TCMP is characterized by (*versus* non-ischaemic/non-valvular DCM)[39] stronger myocardial expression of the major histocompatibility complex class II molecule; particularly potent infiltration of $CD68^+$ macrophages; a general lower presence of T cells and macrophages; increased myocyte size and a lower extent of myocardial fibrosis; and more altered distribution of mitochondrial pattern.

In any case, and considering that PMCT usually presents as HF clinically, it should always be remembered that both supraventricular and ventricular arrhythmias can accompany (overlap) HF regardless of the aetiology (without being its cause) or simply be a consequence of it.[40] Obviously, and in a context of tachycardia, other causes of increased HR must be ruled out (e.g. hyperthyroidism, anaemia) and, as in all cases of HF, baseline natriuretic peptide values must be measured.[1,2,40]

Treatment and prognosis

The main therapeutic objective in patients with TCMP is the normalization of HR either by its reduction or by controlling the rhythm. To achieve this, antiarrhythmic drugs, electrical cardioversion, or radiofrequency ablation can be used.[1,26,40]

For rate control of AF, the drugs of choice are digoxin, amiodarone, β-blockers (e.g. carvedilol and bisoprolol), or calcium channel blockers. For rhythm control, amiodarone is usually preferred. In the case of ventricular arrhythmias, the drugs used are β-blockers or amiodarone.[40] Considering that the impure forms of PMCT are the most frequent, correct HF treatment must be established (according to the guidelines) regardless of the specific treatment of the arrhythmia.[36,40]

In this context and as a consequence of a proper treatment, an improvement in clinical symptoms, recovery of LVEF, and reduction of cardiac volumes are expected (though there may be partial recoveries or failed cases).[6,35,38] Once control of tachyarrhythmia is effective, the greatest improvement in LVEF is found during the first month, whilst its complete recuperation can extend to the second or third month (in general, not more than 6 months).[1,18,41] It has also been observed that patients who present a more significant improvement are those with a worse pre-treatment LVEF[42] whilst, in children, TCMP typically makes a complete recovery with appropriate treatment.[1,43]

Individuals with recovered TCMP can maintain a certain degree of negative remodelling (greater LV volume compared with controls),[44] making these patients more vulnerable to recurrences.[1] This could be related to the persistence of interstitial fibrosis (despite recovery of myocardial function).[45]

Atrial fibrillation

As mentioned above, AF is the arrhythmia most commonly associated with PMCT in adults[15] but is also the most frequently found arrhythmia in patients with HF (regardless of their LVEF). In this complex interplay, it is worth noting that similar risk factors and comorbidities, neurohumoral changes, and structural and electrophysiological alterations create a shared substrate for the development of AF and HF, either independently or concomitantly.[46] Abnormal LV filling pressure in HF with reduced ejection fraction leads to a consequent increase in left atrial pressure and its excessive stretching, whilst mitral regurgitation, if present, further contributes to an increase in intra-atrial pressure favouring the occurrence of AF. Once AF appears, the increased ventricular response, its irregularity and the myocardial contractile asynchrony (all attributable to AF) further compromise LV diastolic filling and intensify the increase in left atrial pressure, which is more pronounced during exercise.[47,48] The progression of HF together with the lack of effective atrial contraction further compromises ventricular filling and, over time, produces cardiac remodelling with progressive dilation of its cavities and functional deterioration in response to the persistent elevation of end-diastolic pressure, forming a vicious circle that predisposes to worsening of both AF and HF.[49]

Left atrial distension in response to high filling pressures leads to promoting intrinsic fibrotic changes, asynchrony in relation to irregular cycles, and inducing cellular ion disturbances (abnormalities in calcium homeostasis), which facilitate and further contribute to perpetuating AF.[50]

Neurohumoral activation, which is classically elevated in HF and directly related to its severity, also promotes structural remodelling with the development of interstitial fibrosis in both atrial and ventricular myocardium. In any case, atrial remodelling predisposes patients with HF to develop AF by altering normal atrial conduction and perpetuate it once installed.[50,51] On the other hand, and since AF and LV systolic dysfunction frequently coexist, despite adequate rate control, it has led to the replacement of the classic name of 'tachycardiomyopathy' by the current term arrhythmia-induced cardiomyopathy.[52]

From the point of view of the general management of AF, the three main goals of therapy are to control symp-

toms, prevent thromboembolism and stroke, and avoid the development of TCMP.[53] Clinically, patients with AF can be treated with an approach of maintaining the abnormal rhythm but controlling its ventricular rate (rate control) or trying to keep the patient in normal sinus rhythm (rhythm control). Rate control is preferably recommended in patients with persistent AF, especially if they have few symptoms.[54] On the contrary, rhythm control is preferred in patients with intermittent (paroxysmal) or highly symptomatic AF, or in the context of an underlying cardiomyopathy.[54]

As previously mentioned, the drugs of choice for frequency control are digoxin, amiodarone, beta blockers (carvedilol, bisoprolol) or calcium channel blockers (verapamil/diltiazem), whilst in the case of rhythm control, amiodarone (class III antiarrhythmic), procainamide (class IA) or flecainide/propafenone (class IC) are preferred. [40,54]

It should be noted that, in general, trials supporting the rate control strategy were designed to assess its non-inferiority compared with rhythm control (not superiority) and were mostly conducted more than 20 years ago.[55] With respect to rhythm control strategies, these may include antiarrhythmic drugs or catheter ablation procedures. The EAST-AFNET 4 trial found that early rhythm control (AF <1 year after diagnosis) regardless of treatment (antiarrhythmic drugs or catheter ablation) was associated with a lower risk of death from cardiovascular causes, stroke, hospitalization for HF or acute coronary syndrome compared with standard care.[56] For its part, the Insights From Get With The Guidelines-Heart Failure registry examined the impact of rhythm control *versus* rate control strategies in patients with HF with preserved ejection fraction and AF. In this case, a lower risk of all-cause mortality at 1 year was documented using a rhythm control approach in patients aged 65 years.[57]

For rhythm control in AF, numerous randomized controlled trials have compared catheter ablation *versus* medical therapy. In the CASTLE-AF study, catheter ablation was associated with a significantly lower rate of a combined outcome of death from any cause or hospitalization for worsening HF in patients with HF (LVEF <35%/NYHA functional class II–IV) and AF in comparison with medical therapy (rate or rhythm control).[58] The AATAC trial showed that catheter ablation was better than amiodarone in preventing recurrence of AF and reducing hospitalization and mortality in patients with HF (LVEF <40%/NYHA II–III) and persistent AF.[59] In the CABANA study, performance of catheter ablation (*versus* medical treatment) did not significantly reduce the primary composite endpoint of death, disabling stroke, major bleeding or cardiac arrest in patients with symptomatic AF. However, the effect of catheter ablation treatment was considered to be limited by lower-than-expected event rates and by treatment crossover.[60] In the STOP AF First trial, pulmonary vein isolation with a cryoballoon (as initial therapy) was found to be better than class I or III antiarrhythmic agents (flecainide, propafenone, dronedarone, sotalol or amiodarone) in preventing recurrence of AF in patients with symptomatic paroxysmal AF.[61] A similar result was found in the EARLY-AF study, in which there was less recurrence of AF with cryoablation *versus* antiarrhythmic drug therapy based on flecainide, propafenone, sotalol, dronedarone or amiodarone in patients with symptomatic, paroxysmal, untreated AF (assessed by continuous heart rhythm monitoring).[62]

The ESC 2020 guideline for the diagnosis and management of AF considers catheter ablation of AF in patients with HF with reduced ejection fraction (class I indication) when there is a high probability that the cardiomyopathy is due to tachyarrhythmia.[63] The 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure for patients proposes AF ablation (level of recommendation 2a) for patients with HF and symptoms caused by AF to improve symptoms and quality of life.[64]

Discussion

Classically, DCM has been defined as a "heart muscle disease characterized by LV or biventricular dilation and systolic dysfunction in the absence of either pressure or volume overload or coronary artery disease sufficient to explain the dysfunction".[65] Despite being caused by various aetiologies and therefore being able to follow different evolutionary courses, DCM continues to be the second most frequent HF phenotype and indication for heart transplantation after ischaemic heart disease.[66] In the case of children and adolescents, DCM represents ~50% of total cases of cardiomyopathy and the main cause of heart transplantation.[67] Within the entire aetiological spectrum of cardiomyopathy in general and the dilated phenotype in particular, there is a heterogeneous group of potentially reversible cardiomyopathies that include TCMP, peripartum cardiomyopathy, inflammatory cardiomyopathy (myocarditis), sepsis-induced cardiomyopathy, thyroid disease-induced cardiomyopathy, Takotsubo cardiomyopathy, cardiomyopathy of chronic diseases (cirrhosis, obesity and uraemia), and alcoholic and some chemotherapy-related cardiomyopathies.[67–70]

As has been mentioned, TCMP is a particular form of reversible cardiomyopathy secondary to incessant or permanent tachyarrhythmia.[1,2] Its prevalence and incidence are difficult to estimate because it can occur in both children and adults[7,8] and, in general, the series analysed have the bias of ablation procedure cases[10–15]

ranging, for example, from 10% in patients with AT to up to 50% in patients with AF.[10,11,15]

From a clinical perspective, TCMP presents as HF associated with dilated cardiomyopathy, usually in the context of or preceded by tachyarrhythmia such as AF, atrial flutter, incessant supraventricular tachycardia, or ventricular arrhythmias (Box 1).[1,2] It was estimated that a HR of ~110–120 bpm is enough to develop the cardiomyopathy,[18,19] and, in this setting, AF represents the leading cause of TCMP in adults,[16] whilst AT and permanent junctional reciprocating tachycardia are such in children.[17]

A close history of preserved LVEF and the absence of LV hypertrophy with a relatively preserved LV end-diastolic diameter (<5.5 cm) can guide the diagnosis of TCMP.[35] TCMP should be differentiated from other forms of non-ischaemic or non-valvular DCM, and, in this context, there are certain elements that may favour its identification, for example, the lack of other apparent underlying causes (for example, hypertension and alcohol abuse).[35]

Spahic et al. retrospectively compared the characteristics of 18 patients with TCMP with 666 patients with non-ischaemic and non-valvular DCM after an episode of HF decompensation. At baseline, AF (or flutter) was present in 78% of patients in the TCMP group, whilst the remaining 22% exhibited other forms of tachycardia or frequent PVCs.[38] In comparison, the ventricular rate was higher in patients with TCMP (122±25 *versus* 78±21; $p<0.001$), whilst their mean ejection fraction was lower (27±12% *versus* 39.0±14.6%; $p=0.001$), though this improved significantly to a greater extent during follow-up (20% *versus* 6%; $p<0.001$). A total of 69% of patients with TCMP underwent cardioversion or ablation.[38] The role of the electrocardiogram and cardiac magnetic resonance in patients admitted for HF with a concomitant supraventricular tachyarrhythmia was assessed by Vera et al. comparing TCMP *versus* other forms of DCM.[37] A total of 43 consecutive individuals with LVEF <50% were analysed; those treated who achieved LVEF >50% during follow-up were classified as TCMP (58%), whilst those (despite receiving treatment) who remained with LVEF <50% were estimated as DCM. Patients with DCM showed wider QRS (121.2±26 *versus* 97.7±17.35 ms; $p=0.003$) with a more frequent presence of late gadolinium enhancement (61 *versus* 16%; $p=0.004$) whereas LVEF was higher in the TCMP group (33.4±11 *versus* 26.9±6.4%; $p=0.019$).[37] A QRS duration ≥100 ms ($p=0.027$), LVEF <40% ($p=0.047$) and presence of late gadolinium enhancement ($p=0.03$) were independent predictors of lack of LVEF recovery (multivariate analysis), whilst, through follow-up (median 60 months), patients with DCM were hospitalized more frequently for HF (44 *versus*, 0%; $p<0.001$) than were patients with TCMP.[37]

Pathophysiologically, the development of TCMP is based on a remodelling process (dilation of the four chambers without parietal hypertrophy), functional deterioration (systolic and diastolic) and an increase in filling pressures[1,2] with underlying neurohormonal overactivation, release of natriuretic peptides, secretion of pro-inflammatory cytokines and alteration of the extracellular matrix. Also present are dysfunctions of excitation–contraction coupling and in the intracellular mitochondrial apparatus, calcium handling and oxidative stress energy production[22–33] (Figure 1). Once HR is normalized (for example, medical treatment, electrical cardioversion and radiofrequency ablation), the clinical and functional recovery of the heart is rapid and does not usually extend beyond 6 months.[1,18,40] However, the possibility of recurrence[1,2,66] exists (unusual in children[42]) possibly linked to the persistence of interstitial fibrosis regardless of LVEF improvement.[43,44]

Montero et al. published a series in which 36 patients (23 men) affected by TCMP (72% AF) were evaluated with a mean follow-up of 3.2±2.9 years. A total of 11 (30%) patients exhibited a deterioration of their LVEF with a median relapse time (from treatment initiation) of 3.08 (0.32–8.03) years due to arrhythmic recurrence or poor control of the original arrhythmia. In these patients, post-relapse LVEF was similar to the original pre-treatment LVEF and those patients treated with ablation of the baseline arrhythmia were non-significantly less likely to have a recurrence regardless of the type of arrhythmia that was ablated; AF as a cause of TCMP, was found to not statistically multiply the relapse risk during follow-up.[71]

As previously mentioned, antiarrhythmic drugs, electrical cardioversion, conventional radiofrequency ablation procedures, or even cryothermal ablation techniques may be required to normalize HR in patients with TCMP.[1,2,6,40,61,62]

Conclusions

TCMP is an unusual and reversible form of HF that usually presents as dilated cardiomyopathy without myocardial hypertrophy and with moderate to severe LVEF impairment in a context of sustained tachyarrhythmia (usually HR >110 bpm). Normalization of HR (regardless of the used resource) is the main therapeutic measure because it usually allows recovery of LVEF and clinical improvement of the individual. The presence of HF in a patient with no prior history exhibiting a persistent tachyarrhythmia should serve as an alert for the clinician or cardiologist. Depending on the severity of the condition, the intensity or type of tachyarrhythmia, more complex therapeutic resources may be required to normalize the HR (e.g. cardioversion, ablation).

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